University of Alberta

CRH and AVP in Depressed Women With and Without Histories of Interpersonal Trauma

by

Tina Marie O'Donnell

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Department of Psychiatry

Edmonton, Alberta
Spring 2008

Library and Archives Canada

Published Heritage Branch

395 Wellington Street
Ottawa ON K1A 0N4
Canada

Bibliothèque et Archives Canada

Direction du Patrimoine de l'édition

395, rue Wellington
Ottawa ON K1A 0N4
Canada

Your file Votre référence
ISBN: 978-0-494-45576-0
Our file Notre référence
ISBN: 978-0-494-45576-0

NOTICE:
The author has granted a non-exclusive license allowing Library and Archives Canada to reproduce, publish, archive, preserve, conserve, communicate to the public by telecommunication or on the Internet, loan, distribute and sell theses worldwide, for commercial or non-commercial purposes, in microform, paper, electronic and/or any other formats.

The author retains copyright ownership and moral rights in this thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without the author's permission.

AVIS:
L'auteur a accordé une licence non exclusive permettant à la Bibliothèque et Archives Canada de reproduire, publier, archiver, sauvegarder, conserver, transmettre au public par télécommunication ou par l'Internet, prêter, distribuer et vendre des thèses partout dans le monde, à des fins commerciales ou autres, sur support microforme, papier, électronique et/ou autres formats.

L'auteur conserve la propriété du droit d'auteur et des droits moraux qui protège cette thèse. Ni la thèse ni des extraits substantiels de celle-ci ne doivent être imprimés ou autrement reproduits sans son autorisation.

In compliance with the Canadian Privacy Act some supporting forms may have been removed from this thesis.

While these forms may be included in the document page count, their removal does not represent any loss of content from the thesis.

Conformément à la loi canadienne sur la protection de la vie privée, quelques formulaires secondaires ont été enlevés de cette thèse.

Bien que ces formulaires aient inclus dans la pagination, il n'y aura aucun contenu manquant.

Canada

ABSTRACT

Interpersonal trauma (IT) is characterized as physical and/or sexual trauma occurring in either childhood or adulthood. In women, the most common response to IT experiences is Major Depressive Disorder (MDD). Comorbid conditions such as Post Traumatic Stress Disorder (PTSD), substance abuse disorders, dissociative disorders, and somatization disorders, among others, have been also observed in female survivors of IT. While the pathophysiology underlying these psychiatric conditions in IT survivors is currently unknown, the Hypothalamic-Pituitary-Adrenal (HPA) axis has been cited in the pathophysiology of both MDD and PTSD. In the current study, plasma levels of corticotrophin releasing hormone (CRH) and arginine vasopressin (AVP) were examined in depressed women with and without histories of IT, as well as in healthy controls. Plasma AVP levels in response to dexamethasone (DEX)-CRH challenge were also examined in all three groups. While no differences in basal CRH or AVP levels were noted between any group, the MDD+IT group had a lower AVP area under the curve (AUC) in response to DEX-CRH challenge compared to healthy controls. No differences in AVP AUC were observed between depressed groups with and without histories of IT. Finally, using the Hamilton Depression Rating Scale (HAM-D) and the Trauma Symptom Checklist (TSC-40), the current study demonstrated that depressed women with histories of IT had more severe MDD as well as a greater number of psychiatric and atypical depressive symptoms compared to the MDD-IT group. The current study suggests that depressed women with histories of IT may have more complex psychiatric and pathophysiological profiles than depressed women without such histories.

ACKNOWLEDGEMENTS

I would first like to thank my supervisor, Dr. Kathy Hegadoren, for her patience, mentorship and encouragement throughout my program. Dr. Hegadoren provided a rich learning environment and gave me numerous opportunities to build upon my strengths and improve upon my weaknesses. Her passion for the field of psychiatry and in particular, stress disorders in women, will not soon be forgotten. I would also like to thank my co-supervisor, Dr. Glen Baker, for his guidance and supervision throughout my graduate education.

Grant support was provided by the Canadian Institutes of Health Research, the Alberta Heritage Foundation for Medical Research, the University of Alberta, the Government of the Province of Alberta and the Department of Psychiatry at the University of Alberta.

Over the years, there were numerous individuals who provided exceptional technical and administrative support: Ms. Gail Rauw, Ms. Jordyce van Muyden, Ms. Jinghong Kang, Dr. Karen Dean, Ms. Saskia de Jager Burford, Ms. Ann O'Neill, Ms. Giselle LeBlanc, Ms. Corina Krause, Ms. Maureen MacAllister, Ms. Jessica Myrholm, Ms. Debbie Kuefler, and Mr. Walter Sumoski. Further, I would like to thank Dr. Nick Coupland and Dr. Anthony Joyce for providing statistical expertise and advice as well as Dr. Jean-Michel Le Melledo for his roles in this project.

I would also like to thank a number of individuals who enriched my education. These individuals include my fellow graduate students, Dr. Gerri Lasiuk, Ms. Kathy Banks, Ms. Evelyn Mitchell, Dr. Kay Rittenbach and Ms. Sarah Cooper. Additionally, I'd like to thank my fellow medical school classmates, Ms. Karli Moncrief, Ms. Erin Thompson, and Ms. Leah Remington, for providing incredible moral support, assistance, and friendship for the final stretch of my PhD, when I often needed to be in two places at once.

Finally, I would like to thank my parents for their love and encouragement over the years. While they are often removed from my academic life, they have truly provided me with the personal tools with which to persevere and succeed.

TABLE OF CONTENTS

LITERATURE REVIEW 1

I. BACKGROUND RELATED TO STUDY POPULATION 1

A. DEPRESSION AND GENDER 3

B. INTERPERSONAL TRAUMA 3

C. DEPRESSION FOLLOWING IT 6

D. PTSD 9

D.1. Prevalence Rates 9

D.2. PTSD and CIT 11

D.3. PTSD and Adult IT 14

D.4. Risk Factors for PTSD 15

D.5. Comorbidity 16

D.6. Complex PTSD 17

D.7. IT and Dissociation 19

D.8. IT and Somatization 21

D.9. IT and Affective Sequelae 24

D.10. IT, Self-Harm and Revictimization 24

E. Summary 26

II. STRESS-RELATED ILLNESS 27

III. PHYSIOLOGY OF STRESS 32

A. Early Work 34

B. HPA Axis 37

C. CRH 39

C.1. Introduction 39

C.2. Synthesis, Location and Pharmacology of CRH 40

C.3. Methodological Considerations 45

D. AVP 47

D.1. Introduction 47

D.2. Synthesis, Location and Pharmacology of AVP 47

D.3. AVP and Stress Models 51

D.4. Methodological Considerations 52

E. Regulation of the HPA Axis 53

E.1. Negative Feedback by Glucocorticoids 54

IV. HPA AXIS AND MDD 56

A. Cortisol Hypersecretion in Depression 57

B. Glucocorticoid Receptors 61

C. The Role of CRH in the Pathophysiology of Depression 62

D. Baseline Levels of AVP in Depression 64

E. Challenge Studies of AVP in Depression 67

F. Conclusions Regarding Dysregulation of the HPA Axis in MDD 68

V. HPA AXIS AND PTSD 69

A. Cortisol Findings in PTSD 69

B. CRH Hypersecretion in PTSD 71

C. AVP 73

VI. HPA AXIS CHANGES IN INTERPERSONAL TRAUMA 74

A. Animal Models of Early Life Stress 74

B. HPA Axis Changes in Individuals Exposed to Interpersonal Trauma 79

B.1. Baseline Cortisol Changes in IT 79

B.2. Psychosocial Challenge Studies of the HPA Axis in IT Survivors 87

B.3. Pharmacological Challenge Studies of the HPA Axis in IT Survivors 90

B.4. Conclusions 94

PURPOSE, OBJECTIVES AND HYPOTHESES OF THE RESEARCH DESCRIBED IN THIS THESIS 96

I. PURPOSE 96

II. OBJECTIVES 98

III. HYPOTHESES 99

MATERIALS AND METHODS 100

I. METHODS 1: RECRUITMENT OF FEMALE SUBJECTS WITH AND WITHOUT MAJOR DEPRESSION FOR PARTICIPATION IN THE DEX/CRH DOUBLE CHALLENGE 100

A. Initial Contact with Participants 100

B. Diagnostic and Psychological Assessment Tools 101

II. METHODS 2: THE DEX-CRH DOUBLE CHALLENGE 104

A. General Timeline of the DEX-CRH Double Challenge 104

B. DEX-CRH Double Challenge 104

III. METHODS 3: MEASUREMENT OF AVP 106

A. Sample Preparation and Extraction of AVP from Plasma 106

B. AVP ELISA 107

IV. METHODS 4: MEASUREMENT OF CRH 109

A. Sample Preparation and Extraction of CRH from Plasma 109

B. CRH RIA 110

V. METHODS 6: MEASUREMENT OF DEXAMETHASONE 111

VI. METHODS 7: MEASUREMENT OF ESTRADIOL AND PROGESTERONE 112

VII. STATISTICAL METHODS 114

ANALYSIS 116

I. DEMOGRAPHIC DATA AND SAMPLE CHARACTERISTICS 116

A. Introduction 116

B. Healthy Controls 117

C. MDD Without History of IT 118

D. MDD With History of IT 118

E. Symptom Severity Scales 120

E.1 Grouped on the Basis of Presence/Absence of IT History 120

E.2 Grouped on the Basis of Presence/Absence of PTSD in IT Group 122

II. AVP 125

A. AVP Analysis with all IT Survivors Grouped Together Regardless of PTSD Diagnosis 125

B. AVP Analysis with IT Group Split into MDD+PTSD and MDD-PTSD 130

III. CRH 135

A. CRH Analysis with all IT Survivors Grouped Together Regardless of PTSD Diagnosis 135

B. CRH Analysis with IT Group Split into MDD+PTSD and MDD-PTSD 136

DISCUSSION 137

I. STUDY OVERVIEW AND CHALLENGES 137

A. Technical Challenges 137

B. Classification of the Depressed Group With Histories of IT 137

II. RATING SCALES 139

A. Hamilton Depression Rating Scale 139

B. Trauma Symptom Checklist 40 141

C. Comparison of the HAM-D and Depression Subscale of the TSC-40 142

III. CRH 143

A. Basal CRH Measurements in Depressed Women With and Without Histories of IT 143

IV. AVP 145

A. Baseline Levels of AVP in Depressed Women with and Without Histories of IT 145

B. AVP Levels Following CRH Challenge in Depressed Women with and Without IT 147

V. SUMMARY OF KEY FINDINGS 150

A. Differences in Psychiatric Profiles in Depressed Women with and without Histories of IT 150

B. CRH in Depressed Women with and without Histories of IT 151

C. AVP in Depressed Women with and without Histories of IT 151

VI. CONCLUSION 152

REFERENCES **156**

LIST OF ABBREVIATIONS

5-HT	5-Hydroxytryptamine; Serotonin
5-HTP	5-Hydroxytryptophan
ABN	Arched Back Nursing
ACTH	Adrenocorticotrophin Hormone
ANOVA	Analysis of Variance
APA	American Psychiatric Association
AVP	Arginine Vasopressin
BDNF	Brain-Derived Neurotrophic Factor
β-END	β-Endorphin
β-LPH	β-Lipotropin
BL	Blank
BNST	Bed Nucleus of the Stria Terminalis
BSA	Bovine Serum Albumin
CIT	Childhood Interpersonal Trauma
CNS	Central Nervous System
CPA	Childhood Physical Abuse
CRH	Corticotrophin Releasing Hormone
CRH_1	Corticotrophin Releasing Hormone-1 Receptor
CRH_2	Corticotrophin Releasing Hormone-2 Receptor
CRH-BP	Corticotrophin Releasing Hormone Binding Protein
CSA	Childhood Sexual Abuse

CSF	Cerebrospinal Fluid
DDAVP	Desmopressin
DESNOS	Disorders of Extreme Stress Not Otherwise Specified
DEX	Dexamethasone
DID	Dissociative Identity Disorder
DSM-III	Diagnostic and Statistical Manual of Psychiatric Disorders, 3rd Edition
DSM-IV	Diagnostic and Statistical Manual of Psychiatric Disorders, 4th Edition
DST	Dexamethasone Suppression Test
EDTA	Ethylenediaminetetraacetic acid
ELISA	Enzyme-Linked Immunoassay
GABA	γ-Aminobutyric Acid
GR	Glucocorticoid Receptor
HAM-D	Hamilton Rating Scale for Depression
HPA Axis	Hypothalamic-Pituitary-Adrenal Axis
HPLC	High Performance Liquid Chromatography
HRP	Horse Radish Peroxidase
IgG	Immunoglobin G
IL-1	Interleukin-1
IL-6	Interleukin-6
IPV	Intimate Partner Violence
IT	Interpersonal Trauma
LC	Locus Coeruleus

LC/MS	Liquid Chromatography/Mass Spectrometry
LG	Licking/Grooming
LSD	Least Significant Difference
MAOIs	Monoamine Oxidase Inhibitors
MDD	Major Depressive Disorder
MR	Mineralocorticoid Receptor
MSH	Melanocyte-Stimulating Hormone
NCS	US National Comorbidity Study
NPY	Neuropeptide Y
NK	Natural Killer
NSB	Non-Specific Binding
NTS	Nucleus of the Tractus Solitarius
NWS	US National Women's Study
PAG	Periaqueductal Gray
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
POMC	Proopiomelanocortin
PSI	Pounds Per Square Inch
PTSD	Post Traumatic Stress Disorder
PVN	Paraventricular Nucleus
RIA	Radioimmunoassay
RM-ANOVA	Repeated Measures Analysis of Variance
RPM	Rotations Per Minute

SCID	Structured Clinical Interview for Diagnosis (DSM-IV)
SD	Standard Deviation
SEM	Standard Error of the Mean
SEP	Separation
SES	Socioeconomic Status
SIDES	Structured Interview for Disorders of Extreme Stress – NOS
SNS	Sympathetic Nervous System
SNRIs	Serotonin-Noradrenaline Reuptake Inhibitors
SSRIs	Selective Serotonin Reuptake Inhibitors
TCAs	Tricyclic Antidepressants
TMB	Tetramethylbenzidine
TNF-α	Tumor Necrosis Factor Alpha
TSC-40	Trauma Symptom Checklist (40-items)
TFA	Trifluoroacetic Acid
TSH	Thyroid Stimulating Hormone
US	United States
V_{1b}	Vasopressin-1b Receptor
WHRU	Women's Health Research Unit

LITERATURE REVIEW

I. BACKGROUND RELATED TO STUDY POPULATION

A. Depression and Gender

The World Health Organization has ranked unipolar major depressive disorder (MDD) second only to ischemic heart disease in terms of global burden of illness (Murray and Lopez, 1997). Data from community samples in established market countries such as the United States (US), Canada, Australia, and Great Britain estimate that approximately 10-25% of women and 5-12% of men experience depression during their lifetimes (Pincus and Pettit, 2001). Prevalence rates of depression among general medical patients have been cited as two to three times higher than that of community samples and are particularly high among inpatients (Kessler et al., 1987; Regier et al., 1993; Coyne et al., 1994). Women are almost twice as likely as men to be hospitalized for depression, which adds to the burden of illness (American Psychiatric Association, 2000).

The prevalence rate of depression is twice as high in women as it is in men (Kessler et al., 1994). Longitudinal studies have demonstrated that gender differences in the prevalence of MDD emerge by age 13 (Choi et al., 1997; Hankin et al., 1998). Over the course of adolescence the gap progressively widens, with prevalence rates of 4.5% and 6.9% at age 15 in males and females respectively, and prevalence rates of 14.1% and 27.5% at age 18 (Hankin et al., 1998; Cyranowski et al., 2000). There has been disagreement over whether gender differences in rates of MDD disappear after women reach menopause. While some studies have demonstrated no gender differences in prevalence rates of MDD following child-bearing years in women (Brown et al., 1992;

Meller et al., 1987), others have found that the 2:1 ratio remained constant following menopause (Bijl et al., 1998; Zunzunegui et al., 1998).

No differences in the severity of depressive symptoms have been reported between men and women (Frank et al., 1988; 1994; Young et al., 1990), but gender differences appear to exist in the clinical presentation of symptoms, the course of the depressive illness, and in the types of comorbid psychiatric disorders. Women are more likely to present clinically with atypical symptoms such as hypersomnia, weight gain, carbohydrate craving and hyperphagia (Carter et al., 2000; Burt and Stein, 2002; Angst, 2002). Additionally, women tend to report a greater degree of distress, number of symptoms, and functional impairment in occupational and familial roles (Frank et al., 1988; Young et al., 1990; Leibenluft et al., 1995; Kornstein et al., 2000).

Greater chronicity and episode recurrence have also been observed in women (Kornstein et al., 2000). Since the risk of recurrence increases over time and with each subsequent depressive episode (Lavori et al., 1994), it is particularly important that women be treated aggressively for symptoms of MDD. Finally, women are more likely to suffer from comorbid anxiety disorders, such as panic disorder or post traumatic stress disorder (PTSD) while men are more likely to experience comorbid substance abuse disorders (Kessler et al., 1994; Rapaport et al., 1995).

A number of cultural, psychosocial, and biological theories have been put forth to explain gender differences in the prevalence of MDD. Common explanations point to differences in personality traits between men and women (Goodwin and Gotlib, 2004), pre-existing anxiety (Breslau et al., 1995), ruminative coping styles in women (Nolen-Hoeksema et al., 1999), female sex hormones (Parry, 1989), gender differences in types

of major life traumas (Brand, 2004) and higher rates of chronic strain caused by greater poverty and limitations in social power and status amongst women (Goodwin and Gotlib, 2004).

Higher rates of interpersonal trauma (IT; sexual or physical abuse) in both childhood and adulthood have been reported in women and are considered important contributors to the elevated prevalence rate of MDD in women. In fact, the most commonly reported response to serious childhood stressors or traumatic events in women is depression (Browne & Finkelhor, 1986; Kendler et al., 1993; Veijola et al., 1998). Indeed, it has been suggested that the differences in rates of MDD in adult men and women are attributable to higher rates of childhood sexual abuse (CSA) and intimate partner violence (IPV) in women (Campbell, 2002).

B. Interpersonal Trauma

IT is increasingly recognized as a contributor to negative health outcomes in the general population. In particular, IT has been associated with increased health care utilization and costs (Felitti, 1991; Arnow et al., 1999). IT is operationally defined in this thesis as (1) sexual contact occurring against the will of the person under threat of coercion, violence, or use of physical force by parents, spouses, relatives, friends or acquaintances, (2) physical abuse where parents, spouses, relatives, friends or acquaintances commit acts that result in physical injury, or (3) a combination of both sexual and physical abuse (Russell, 1986; Briere, 1992; Weaver and Clum, 1996; Hegadoren et al., 2006). This definition does not encompass other forms of abuse that

have been shown to contribute to adult mental health problems such as emotional neglect (Widom, 1999; Spertus et al., 2003) and also excludes non-contact sexual experiences.

While the prevalence and long-term effects of IT in childhood and adulthood are thought to be significant, the methodology and populations used in such studies are often suspect. Unfortunately, many acts of IT go unreported and thus, our knowledge of the acute and long-term effects of IT on health outcomes is limited to individuals who are willing to disclose trauma histories and to those who agree to participate in research studies. For example, one study found that only 2% of sexually abused women discussed their victimization history with their physicians (Springs and Friedrich, 1992). Further, investigations examining the prevalence of IT among community and clinical populations of children and adults have been subject to a number of confounding variables such as differing data sources (social agencies, health care institutions, universities, community settings, etc), small sample sizes, non-standardized methods of data collection, and differing definitions of trauma. Briere and Elliot (2003) cited four primary criticisms of past studies examining IT: (1) most studies use either purely clinical samples or university samples that do not reflect rates of child abuse in the general population, (2) generic and non-standardized methods of data collection may not adequately capture psychiatric symptoms arising from childhood trauma, (3) many studies do not study sexual and physical abuse separately and thus the true impact of each type of trauma is unknown, and (4) confounding variables related to demographic, socioeconomic, and familial factors may complicate the interpretation of abuse-related vs non-abuse related effects.

With these criticisms in mind, a number of studies have attempted to assess the prevalence of IT in both adulthood and childhood. A select number of childhood interpersonal trauma (CIT) studies are summarized in Table 1.

Table 1: Prevalence Rates of CIT

Reference	Country of Origin	N	Type of IT	Prevalence Rate in Women	Prevalence Rate in Men
Finkelhor et al., 1990	US	2626	CSA	27%	16%
Macmillan et al., 1997	Canada	9953	CSA	12.8%	4.3%
Briere and Elliot, 2003	US	1442	CSA	32.3%	14.2%
Putnam, 2003	All English-language articles (1989-1999)	-	CSA	16.8%	7.9%
Macmillan et al., 1997	Canada	9953	Childhood physical abuse (CPA)	21.1%	31.2%
Briere and Elliot, 2003	US	1442	CPA	19.5%	22.2%
Macmillan et al., 1997	Canada	9953	CPA+CSA	6.7%	2.4%

Most studies examining the prevalence of adult IT in women often target specific vulnerable populations or collect data that examine lifetime prevalence of IT in both childhood and adulthood. However, a few studies have examined the prevalence of adulthood IT exclusively. These studies are summarized in Table 2.

Table 2: Prevalence Rates of Adulthood IT

Reference	Country of Origin	N	Type of IT	Prevalence Rate in Women	Prevalence Rate in Men
Cloutier et al., 2002	US	2109	Sexual assault	19%	-
Elliot et al., 2004	US	941	Sexual assault	22%	3.8%
Amar and Genarro, 2005	US	?	Physical violence	48%	-
Wilt and Olson, 1996	Estimation in general population		Domestic violence	10-15%	-

The relationship between CIT and adult mental health complications has been a contentious issue in that experts argue that other pathogenic factors (eg. family environment, adult incidents of trauma, psychological neglect) may contribute to the development of psychiatric sequelae (Rumstein-McKean and Hunsley, 2001). Concerns regarding the appropriateness of research designs, diagnostic and data collection tools, and the timing of assessments are cited as possible confounding variables in studies examining the impact of CIT on adult mental health. Rumstein-McKean and Hunsley (2001) also cited concerns over the manner in which clinicians and researchers generalize conclusions regarding mental health outcomes in survivors of IT from clinical populations to community samples and vice versa. In order to fully understand the impact of IT on mental health outcomes, it must be recognized that individuals who seek mental health services are likely to be more severely affected than those who do not. Thus, while it is important to understand the nature, range, chronicity, and severity of problems resulting from IT in clinical populations, researchers should recognize that the most severe cases will not be representative of those who have experienced IT (Rumstein-McKean and Hunsley, 2001). Conversely, individuals who show limited signs of psychiatric sequelae in the aftermath of IT are in no way representative of clinical populations.

C. Depression Following IT

MDD has been cited as the most common response to childhood traumas in women (Browne and Finkelhor, 1986; Broadhead and Abas, 1998; Veijola et al., 1998; Kendler et al., 2000; Putnam, 2003; Arnow, 2004). A history of CSA has been associated

with earlier onset of depressive symptoms and prolonged durations of depressive episodes (Zlotnick, 2001). A study by Zuravin and Fontanella (1999) evaluated 11 markers of family dysfunction in 513 low-income women, including 105 who had experienced CSA; those with CSA were three times more likely to develop MDD. Thus, while it has been argued that MDD in adult survivors of childhood abuse may be a symptom of general dysfunction within families where abuse occurs rather than a direct result of the abuse itself, the study by Zuravin and Fontanella (1999) suggests otherwise.

Researchers have examined which elements of CSA are the most strongly correlated with the development of MDD in adulthood. Abuse perpetrated by a father figure appears to have a significant impact on the future development of MDD in adult survivors of CSA (Roesler and McKenzie, 1994), while the use of force by non-father figures is significantly related to the presence of depression in sexually abused girls (Johnson et al., 2001). Other data strongly suggest correlations between greater severity, frequency and duration of abuse in childhood and the later development of MDD in adulthood (Sedney and Brooks, 1984; Briere and Runtz, 1988; Arnow, 2004).

Adult IT has also been found to contribute to the development of MDD in women. A study by Bifulco et al. (1991) found that in women who had experienced forced intercourse, MDD occurred 100% of the time. Repeated sexual abuse not involving intercourse resulted in MDD in 78% of women, while a single incident of sexual abuse not involving intercourse resulted in MDD in 30% of women. Another study noted that lifetime prevalence rates of MDD in women following one rape were approximately 46% and about 80% following multiple rapes (Kilpatrick et al., 1988).

MDD and PTSD are the most common mental health outcomes associated with IPV (Campbell and Soeken, 1999). According to a review by Campbell (2002), some women who experience IPV may have pre-existing chronic MDD, which is exacerbated by violent episodes, but evidence also suggests that MDD can be triggered by such episodes and even diminish with decreasing IPV (Campbell and Soeken, 1999).

In addition to MDD and PTSD, it has been well documented that both childhood and adulthood IT are associated with a wide spectrum of Axis I and Axis II disorders. These include anxiety disorders, dissociative identity disorders (DID), sleep disorders, somatization disorders, substance abuse disorders, eating disorders, and borderline personality disorder (Bryer et al., 1987; Bifulco et al., 1991; Pribor and Dinwiddie, 1992; Hall et al., 1993; Young et al., 1997; Campbell, 2002; Kendall-Tackett, 2002). In children, sexual and/or physical abuse is also associated with early behavioral problems and conduct disorders, which may be associated with an increased propensity to engage in risky behaviors that may put the individual at heightened risk for further traumatic episodes (Widom, 1999).

A history of sexual and physical abuse is associated with increased severity of psychiatric symptoms (Zlotnick, 1996). Additionally, there may be a dose-response relationship between the severity of and duration of the trauma and the development of psychiatric sequelae such as MDD and PTSD (Golding, 1999). For example, CSA is more likely to predict the development of future psychiatric illness than sexual assault occurring in adulthood (Burnam et al., 1988). Additionally, individuals who have experienced multiple traumatic episodes are likely to have poorer health outcomes than singly traumatized individuals (Norris and Kaniasty, 1994). While a large portion of

women with histories of IT will initially be diagnosed primarily with MDD, additional comorbid psychiatric diagnoses are likely.

D. PTSD

PTSD has long been considered a heterogeneous disorder (Kolb, 1989). As a diagnostic category, PTSD was developed in response to patterns of symptoms following stressful life events. According to the DSM-IV, PTSD involves three main clusters of symptoms involving re-experiencing of the traumatic event, avoidance of trauma cues or reminders, and hyperarousal (American Psychiatric Association, 1994). A broad spectrum of psychiatric conditions may result from IT, with MDD and PTSD being the most frequently studied outcomes. Unfortunately, the complexity of trauma-related psychiatric sequelae in female survivors of IT, particularly in survivors of CIT, is not accurately reflected in the diagnostic criteria represented by PTSD. As discussed in later sections, several authors have suggested that an expanded diagnostic concept is necessary to fully encapsulate the mental health issues experienced by some survivors of CIT.

D.1. Prevalence Rates

PTSD was originally defined as a psychiatric diagnosis in 1980 (DSM-III) in response to symptoms observed in male combat veterans of the Vietnam conflict. Therefore, much of the initial research surrounding the epidemiology, biology, and treatment of PTSD focused on data obtained using this group. Since those initial studies, our knowledge of PTSD has evolved substantially. The prevalence rate of PTSD following trauma has been estimated to be about 25% (Breslau et al., 1991; Green, 1994).

For traumatic events that are considered life-threatening, prevalence rates are much higher (Kessler et al., 1995). Lifetime prevalence rates of PTSD have been assessed at 7-9%, with community rates of lifetime exposure to trauma estimated at 40-80% (Seedat and Stein, 2000).

As with MDD, gender differences in the prevalence of PTSD have been noted. A number of studies have demonstrated that the prevalence of PTSD is twice as high in women as it is in men (Helzer et al., 1987; Breslau et al., 1991; Davidson et al., 1991; Green et al., 1994; Kessler et al., 1995; Bromet et al., 1998). Gender differences in PTSD cannot be accounted for by increased exposure to trauma in women since, with the exception of sexual traumas, men experience trauma more often than women (Breslau et al., 1991; 1998; Kessler et al., 1995). Differences in the rates of exposure to specific types of trauma may partially account for gender differences in the prevalence of PTSD. Stein and colleagues (2000) found that women were at increased risk of developing PTSD following assaultive violence (e.g. being attacked, robbery, mugging, being threatened with a weapon) but not following non-assaultive violence (serious motor vehicle accident, fire, natural disaster, witness to a severe injury). This is supported by data showing women to be 6-15 times more likely to develop PTSD following assaultive violence that is not sexual in nature (Breslau et al., 1998; Kessler et al., 1995).

In addition to being at higher risk for developing PTSD following assaultive forms of violence, women were 4 times more likely than men to develop chronic PTSD where symptoms of PTSD linger for at least one year following the initial trauma (Breslau et al., 1991). Interestingly, another study by Breslau (1998) demonstrated that the median duration of PTSD symptoms was 48.1 months for women and 12.1 months

for men while the median time for remission of PTSD symptoms was 35 months for women and 9 months for men. These studies lend support to the idea that different psychosocial and/or biological mechanisms may be at work in the development and maintenance of PTSD symptoms between the genders and highlight the importance of studying each gender separately.

D.2. PTSD and CIT

Sexual and physical violence in either childhood or adulthood are commonly associated with the development of PTSD symptoms in women (Davidson et al., 1991; Kessler et al., 1995; Brewin et al., 1999). Many children develop PTSD as a result of sexual abuse (Wolfe et al., 1994), but chronic PTSD delayed until adulthood is also a common sequelae of CSA.

Generally, studies examining the link between CIT and prevalence rates of PTSD have involved convenience samples. These studies predominantly fall into one of three categories: (1) retrospective studies of adults examining the extent of PTSD in the community (usually samples of college women) by inquiring about prior child victimization, (2) psychiatric assessments of abused children seen in a medical or governmental setting, and (3) psychiatric assessments of adults with histories of childhood IT seeking treatment in health clinics or voluntarily participating in studies that call for volunteers with histories of IT.

Several small studies examining the prevalence of PTSD in clinical populations of women who experienced sexual abuse as children observed prevalence rates ranging from 20-100% (Lindberg and Distad, 1985; Greenwald and Leitenberg, 1990). In a study

examining lifetime prevalence of PTSD, Rodriguez and colleagues (1996) found that 86% of adults (n=117) who experienced CSA presenting in medical clinics met full diagnostic criteria for PTSD at some point in their lives. In those individuals who do seek treatment, women appear to be particularly vulnerable to developing PTSD after CSA, where symptoms from events occurring in childhood contribute to the same level of functional impairment as those observed in adult survivors of abuse (Mulvihill, 2005; Cromer and Sachs-Ericsson, 2006).

The recent US National Women's Study (NWS) surveyed 3220 women regarding whether they had experienced at least one instance of forcible sexual penetration before the age of 18 (Ruggiero et al., 2004). Of the group that disclosed they had experienced childhood rape (n=288; 8.9%), 23.6% met full PTSD criteria in the previous year while 47.2% had re-experiencing symptoms, 29.5% experienced avoidance symptoms, and 36.7% met hyperarousal criteria. Thus, while full PTSD diagnostic criteria may not be currently met in women with histories of CSA, they may still experience PTSD-related symptoms. These symptoms may be exacerbated in times of stress or as a result of further trauma, leading to full PTSD diagnoses. A Canadian survey found that 9% of women who had experienced CSA had either full or partial PTSD symptoms at the time of the study (Stein et al., 2000). Differences between this study and the NWS are likely due to the inclusion of forms of sexual abuse other than forcible penetration in the Canadian study since penetration is considered one of the most invasive forms of sexual abuse and is strongly associated with PTSD prevalence and severity (Saunders et al., 1992).

In an attempt to predict the development of PTSD in survivors of CIT, researchers have examined specific characteristics such as the age of onset of abuse, the

relationship between the victim and perpetrator, the number of perpetrators, the duration of abuse, and the severity of abuse. Younger age of onset, longer duration of abuse, and more frequent incidents of abuse have all been associated with increased risk of developing PTSD symptoms (Wolfe et al., 1994; Rodriguez et al., 1996, Saunders et al., 1992). The degree of trust the victim had in the perpetrator has been positively correlated with PTSD symptoms, with family members, such as a father or step-father, potentially invoking the most trauma (Beitchman et al., 1992; Browne and Finkelhor, 1986; Ullman, 2007). Additionally, higher numbers of perpetrators have been significantly correlated with lifetime PTSD severity (Briere and Runtz, 1989; Rodriguez et al., 1996). Finally, the dynamics of abuse appear to play a role in the future development of PTSD. Penile penetration, which represents one of the most invasive acts, has been strongly associated with PTSD severity and prevalence (Epstein et al., 1997).

A link between CPA and the development of adult PTSD has been suggested. A large study of adult women (n= 4009) by Duncan and colleagues (1996) found a lifetime PTSD prevalence rate of 54% and a current PTSD prevalence rate of 33% following childhood physical abuse. This compares to lifetime rates of 11% and current prevalence rates of 4% in women who did not experience CPA. Another study observed current PTSD prevalence rates of 11.2% for CPA, 16.2% for CSA, and 53.4% for adults who experienced both sexual and physical abuse as children (Schaaf and McCanne, 1998). Differences in prevalence rates between the two studies may be explained by the fact that Duncan et al. (1996) used a general population sample, while Schaaf and McCanne (1998) surveyed university students. Since university students may be, on average, higher functioning and less affected by previous abuse, the results may not be an accurate

reflection of the general population as a whole. Regardless, children who experience both sexual and physical abuse are at the highest risk of developing PTSD and other psychiatric sequelae as adults (Ackerman et al., 1998).

D.3. PTSD and Adult IT

There is some discrepancy regarding the prevalence of PTSD in women following sexual and nonsexual assault. Rothbaum and colleagues (1992) reported that 94% of rape survivors and 71% of nonsexual assault developed PTSD symptoms within two weeks of the traumatic event (Rothbaum et al., 1992). This same study reported that three months later, 47% of rape survivors and 21% of survivors of nonsexual traumas had PTSD diagnoses. Another study observed PTSD in 80% of women who reported the sexual assault (Breslau et al., 1991).

Studies examining PTSD in women with IPV histories found prevalence rates ranging from 33% to 58% (Houskamp and Foy, 1991; Astin et al., 1993; 1995; Coker et al., 2005). Differences in prevalence rates of PTSD among these studies may be explained by the time passed since the last domestic abuse episode, population sampling (e.g. community, women's shelters), and differences in assessment instruments and data collection methods. Mertin and Mohr (2001) found that women who develop PTSD as a result of IPV reported experiencing higher levels of violence, were more likely to have a spouse with a substance abuse problem and were more likely to believe they would be killed by their spouse than women who did not meet criteria for PTSD. Finally, a study by Woods (2000) observed that 44-66% of 52 women surveyed still experienced PTSD symptoms nine years after leaving an abusive relationship.

D.4. Risk Factors for PTSD

Taken together, experiences of IT such as CSA and CPA, as well as IPV, rape and adult assaultive violence are strongly associated with either partial or full PTSD diagnoses. Wong and Yehuda (2002) cited a number of risk factors for the development of PTSD. These include gender, severity of trauma (Foy et al., 1984; Yehuda et al., 1998), a history of stress, abuse, or trauma (Bremner et al., 1997; Zaidi and Foy, 1994), a history of behavioral or psychological problems (Helzer et al., 1987), pre-existing psychiatric disorders (McFarlane, 1985), a family history of psychopathology (Davidson et al., 1985), genetic factors (True et al., 1993), subsequent exposure to reactivating environmental factors (McFarlane, 1989; Schnurr et al., 1993), initial psychological reaction to trauma such as emotional numbing (Epstein et al., 1998; Feinstein and Dolan, 1991; Mayou et al., 1993; Shalev et al., 1996) and early separation (Breslau et al., 1991; McFarlane, 1988). Zoellner and colleagues (1999) also implicated several risk factors not included by Wong and Yehuda (2002) that may determine why female assault victims develop chronic PTSD. These include the severity of initial PTSD symptoms (Foa et al., 1995), assailant identity (Cascardi et al., 1996), depression (Shalev et al., 1997), general anger and blame in the aftermath of the assault (Riggs et al., 1992) and degree of social support following the assault (Ullman and Siegel, 1994). Degree of social support as a risk factor for the development of PTSD has been disputed by Zoellner et al. (1999), who demonstrated that interpersonal friction in the immediate aftermath of trauma (ie within 2 weeks) but not positive social support determined PTSD severity 3 months later. These results are consistent with several other studies which found that negative reactions to

disclosure rather than positive ones were more predictive of symptom severity (Davis et al., 1996).

D.5. Comorbidity

While PTSD is an Axis I psychiatric disorder, it seldom occurs independent of other psychiatric sequelae. According to the National Comorbidity Survey (NCS) in the US, PTSD commonly occurs with at least one other psychiatric diagnosis and a substantial percentage of individuals have at least 3 or more other psychiatric diagnoses (women – 44%; men – 59%). Only 21% of women and 12% of men have no other psychiatric diagnosis other than PTSD (Kessler et al., 1995). One of the more common psychiatric diagnoses that occurs with PTSD in women is MDD. In fact, the NCS observed comorbidities of MDD and PTSD in 49% of women and 48% of men (Kessler et al., 1995). This evidence is supported by a study that followed a group of trauma survivors from their initial appearance in the emergency room and found that at 4 months post-trauma, 17.5% met criteria for PTSD, 14.2% met criteria for MDD, and 43.2% met criteria for both PTSD and MDD (Shalev et al., 1998). Another study found that 53.2% of motor vehicle crash survivors had both PTSD and MDD three months after the accident (Blanchard et al., 1998).

It is well recognized that individuals with comorbid MDD and PTSD have higher levels of functional impairment and greater symptom severity than individuals with either MDD or PTSD alone (Shalev et al., 1998; Blanchard et al., 1998). Additionally, individuals with comorbid MDD and PTSD are more treatment resistant and less responsive to antidepressant therapies and/or psychotherapeutic intervention (Brady et

al., 2000). Based on these clinical observations, the co-occurrence of both illnesses leads to a clinical state that is more severe than either illness individually.

Comorbidity with PTSD may not only lead to greater functional impairment and symptom severity but may also contribute to a prolonged course of illness. The NCS found that approximately one third of individuals with PTSD had symptoms that failed to remit after 6 or more years (Kessler et al., 1995). Chronic PTSD has been associated with affective disorder comorbidity (Breslau et al., 1991), childhood trauma (Zlotnick et al., 1999), and substance abuse (Zlotnick et al., 1999; Mueser et al., 2004).

In addition to its association with MDD, PTSD has been associated with substance abuse disorders following trauma (Davidson et al., 1990; Najavits et al., 1997; 1998). A history of IT, particularly CSA and CPA, has been associated with substance abuse (Saylors and Daliparthy, 2006) and use of substances such as opiates (Heffernan et al., 2000), crack (Young et al., 2002), alcohol (Clark et al., 1997; Zlotnick et al., 2007), and cocaine (Najavits et al., 1997; 1998), among others (Ullman et al., 2006). Female survivors of IT with PTSD and substance disorders have higher treatment resistance, higher levels of psychological impairment, more complicated symptom structures, and higher rates of revictimization than those with PTSD alone (Gil-Revas et al., 1996; Ullman et al., 2006; Schumacher et al., 2006).

D.6. Complex PTSD

Since the DSM-III-R criteria for PTSD placed emphasis on a single circumscribed event, clinicians and researchers who work with survivors of prolonged and repeated trauma recommended that a complex post-traumatic syndrome named *Disorders of*

Extreme Stress (DESNOS) or complex PTSD be included in the DSM-IV to encompass the diverse range of symptoms observed in these individuals. Examples of prolonged trauma include prisons, concentration camps, religious cults, circumstances of organized sexual exploitation, and prolonged abuse within families (Herman, 1997). As stated in the DSM-IV guidebook (1995), DESNOS was not included in the DSM-IV for the following reasons: (1) most studies and clinical reports were retrospective and uncontrolled, leading to considerable bias and methodological problems in linking conditions of extreme stress to psychopathology and (2) many victims of extreme stress do not develop subsequent psychopathology and, thus, a cause-effect relationship needs to be more carefully delineated. While this conservative stance by the American Psychiatric Association (APA) provides rationale for not including DESNOS in the DSM-IV, evidence exists to suggest that the current diagnostic criteria for PTSD does not fully encapsulate the clinical experience of survivors of IT. Clinical reports suggest that some female survivors of childhood abuse in particular may indeed have psychopathology that is not easily categorized by current diagnostic formulations and that DESNOS best accounts for symptoms observed in adult survivors of childhood abuse (Zlotnick et al., 1996; Pelcovitz et al., 1997; Ford and Kidd, 1998). Some survivors of IPV also appear to have a diverse subset of symptoms that are unique in both their severity and tenacity that are not characterized by current DSM-IV criteria (Woods and Campbell, 1993; Smith and Gittelman, 1994; Dickinson et al., 1998; McNutt et al., 2002).

Intense and prolonged childhood abuse, IPV, and repeated sexual victimization are just a few examples of situations where IT can take the form of prolonged, repeated trauma resulting in extraordinary psychiatric sequelae. Judith Herman (1997) cited three

key areas where a PTSD diagnosis was not sufficient to describe symptoms in survivors of prolonged trauma: (1) symptom dynamics – symptoms are more numerous, complex, and disruptive, (2) personality changes – deformations regarding identity and relatedness, and (3) vulnerability to repeated harm by self and others.

Clinicians who work with survivors of prolonged and/or repetitive IT have characterized their post-trauma state as one complicated by chronic depression, anxiety, dissociative symptoms, sleep problems, impulsivity, personality disruptions, self-harm, suicidality, ego fragmentation, revictimization, and somatization (Gelinas, 1983; Bryer et al., 1987; Briere et al., 1988; Briere and Runtz, 1988; Herman, 1997; Lechner et al., 1993; Zlotnick et al., 1996; Allen et al., 1999; Steiner et al., 2003). Many of these psychiatric symptoms transcend a simple diagnosis of PTSD. For severely affected women who have experienced repeated childhood abuse, IPV, or IT, three key categories of symptoms not associated with a diagnosis of PTSD may occur. These include dissociative symptoms, extensive somatization and physiological reactivity, and affective sequelae (Herman, 1997). Each will be described in detail below.

D.7. IT and Dissociation

The DSM-IV defines dissociation as a defense that "deals with emotional conflict or external and internal stressors with a breakdown in the usually integrated functions of consciousness, memory, perception of self or the environment, or sensory/motor behavior" (APA, 1994). For most people, dissociation is an everyday event associated with daydreaming or fleeting trance-like states that are easily controlled and prompted at will. During periods of stress or trauma, however, dissociation may become a defense

against experiences that the mind cannot fully integrate. In situations where danger is imminent, the mind may fragment the experience to initiate "automatic", sub-cortical reactions, leading to escape, freezing behavior, or other adaptive mechanisms without allowing the mind to fully integrate the experience into consciousness and memory. While such a response may be valuable during periods of acute danger, it may become pathological if it persists too long or intensely or occurs in situations where no real danger exists. In these situations, dissociation may become a clinical construct as reflected by alterations in memory where aspects of the trauma are not accessible to the individual. Additionally, alterations in both identity and consciousness may occur. Reduced physiological reactivity and cognitive processing may occur as a result of altered consciousness, leading to incomplete physiological and cognitive responses in the presence of adverse stimuli. This was demonstrated by Griffin and colleagues (1997), who observed significant suppression of autonomic responses in survivors of rape who experienced peritraumatic dissociation. Compared to the group of rape survivors who had low levels of peritraumatic dissociation, the high dissociation group contained a much greater proportion of women meeting criteria for PTSD.

Controlled studies linking dissociative phenomena and PTSD in survivors of childhood abuse are lacking. Because of its ties to Multiple Personality Disorder, Dissociative Identity Disorder (DID) has been considered a controversial diagnosis and thus, few studies linking it to PTSD have been carried out. Peritraumatic dissociative symptoms during CSA have also been shown to lead to more frequent and severe PTSD symptoms later in life (Marmar et al., 1994; Koopman et al., 1994). Bremner and colleagues (1998) noted PTSD prevalence rates of 86% in 35 individuals who met DSM-

IV criteria for one or more dissociative disorders. Other clinical studies report a strong relationship between PTSD and dissociative phenomena in survivors of severe childhood abuse (van der Kolk et al., 1996; Chu et al., 1999), while CSA, physical neglect, and emotional abuse are significant predictors of a dissociative disorder diagnosis (Sar et al., 2007). Further research is necessary to elucidate the prevalence of dissociative symptoms in female survivors of IT with PTSD. Since many survivors of IT with dissociative symptomology may not meet full criteria for one or more of the DIDs, the identification of past or present dissociative symptoms in survivors of IT is necessary if we are to understand the relationship between dissociation and PTSD in these individuals. The past or current presence of dissociative symptoms without a full dissociative diagnosis is likely to affect the treatment of other mental health problems such as PTSD and MDD, among others in survivors of IT. Further, peritraumatic dissociation is predictive of PTSD severity (Marmar et al., 1994; Koopman et al., 1994) and thus, in individuals with partial or full PTSD diagnoses, revictimization will likely exacerbate an already complicated diagnosis.

D.8. IT and Somatization

According to the DSM-IV, somatization disorder is characterized by the presence of several somatic symptoms that cannot be explained on the basis of physical, medical and diagnostic examinations. Somatic complaints usually involve multiple organ systems and symptoms disclosed by the individual may be specific or diffuse. In most individuals, the disorder is characterized as chronic and is associated with impaired social and occupational functioning, psychological distress, and extensive help-seeking behavior.

Since individuals with somatization disorder may seek out multiple health practitioners, it is thought to be underdiagnosed in the general population. However, it has been demonstrated that in women, the lifetime prevalence rate may be 1 to 2% (APA, 1994) and that the prevalence rate may be five times higher in women than it is in men (APA, 1994). While a discussion regarding the etiology of somatization disorder is beyond the scope of this thesis, previous research suggests strong associations between specific or multiple episodes of trauma and somatic complaints.

Individuals with PTSD demonstrate more somatization symptoms than healthy controls without a PTSD diagnosis (Shalev et al., 1990; McFarlane et al., 1994; Zlotnick et al., 1996; Andreski et al., 1998) or individuals with another psychiatric diagnosis (Escobar et al., 1987; Andreski et al., 1998). Individuals who experience multiple episodes of trauma and subsequently develop chronic PTSD appear to be at particular risk for developing comorbid somatization disorder (Davidson et al., 1991). Additionally, the severity of PTSD symptoms appears to be directly correlated to the severity of physical health problems (Kimerling et al., 2000; Zoellner et al., 2000). Deering and colleagues (1996) have suggested that trauma involving physical suffering would most likely lead to somatization and that physical distress experienced during the trauma would become strongly connected to the development of PTSD symptoms.

Most research linking PTSD and somatization has examined combat veterans and thus the current state of the literature reflects this bias. It has been increasingly acknowledged, however, that women with histories of chronic or repeated IT may also present clinically with complex forms of somatization. In particular, IT has been associated with poorer perceived health outcomes (Felitti et al., 1998; Dickinson et al.,

1999; Dube et al., 2003; Stein et al., 2004), increased utilization of health care services (Koss et al., 1991; Suris et al., 2004) and more surgical procedures (Radomsky, 1992). In addition to accessing mental health services, survivors of IT frequently report distress regarding a wide spectrum of physiological complaints. These include, but are not limited to, chronic pain (Campbell, 2002), headache (Felitti et al., 1998; Golding, 1999; Arnow et al., 2000), pelvic pain and gynecologic issues (Golding et al., 1998; Wijma et al., 2003) and gastrointestinal difficulties (Roberts, 1996; Campbell, 2002). Domestic violence studies report both acute injuries and long-term health consequences of abuse (Eby et al., 1995; Plichta, 1996; Golding et al., 1997; Tollestrup et al., 1999), in addition to mental health problems such as MDD and PTSD, among others.

Since most studies have examined somatic phenomena in clinical populations, the prevalence and severity of somatic symptoms associated with IT in the general population is unknown. Present research suggests that female survivors of IT, particularly childhood abuse and IPV, have a high rate of health services utilization (Koss et al., 1991; Radomsky, 1992; Suris et al., 2004). However, this research likely reflects survivors of IT who have been the most severely physically affected by their experiences without providing insight regarding which aspects of the abuse have resulted in somatic complaints. Many studies examining health care utilization and/or specific somatic symptoms do not investigate the presence of potential comorbid psychiatric symptoms. Thus, while it has been suggested by Herman (1997) that survivors of repeated abuse may present clinically complex symptoms not associated with the current DSM-IV diagnosis of PTSD, it is uncertain how these findings are related to a complex PTSD

diagnosis. Further research in general medical clinics should expand upon these data to include questions about mental health status.

D.9. IT and Affective Sequelae

In female survivors of prolonged IT, a description of the affective sequelae associated with a complex post-traumatic syndrome proves to be the most troublesome of the three key symptom clusters not associated with PTSD. Because many survivors of IT do not initially disclose abuse histories to their health care providers, diagnoses are made based on either self-disclosed or observed symptoms. In the absence of information related to trauma history, a number of diagnostic constructs have been used by clinicians to characterize affective changes in female survivors of IT. These include, but are not limited to MDD, dysthymic disorder, bipolar II disorder, adjustment disorder with mood features, and/or borderline personality disorder. Unfortunately, none of these specific DSM-IV diagnoses appears to fully encapsulate the symptoms experienced by severely affected survivors of prolonged IT. Affective sequelae observed in survivors of severe IT may include episodic or chronic depression, mood reactivity, anger management problems, alexithymia, irritability, impulsivity, anxiety, self-injurious behaviors, and the inability to self-soothe (van der Kolk and Fisler, 1994; Zlotnick et al., 1997).

D.10. IT, Self-Harm and Revictimization

There is an accumulating body of evidence to suggest that survivors of childhood abuse are at heightened risk of revictimization, either self-inflicted or by others. Self-inflicted revictimization may take the form of recurrent re-experiencing of traumatic

events caused by recollections, thoughts, or images of trauma, trauma-associated internal or external cues, interaction with persons involved, and nightmares, among others. Some survivors of severe childhood abuse are known to participate in self-injurious behaviors such as cutting themselves with knives, razor blades, or other sharp objects.

Protracted histories of sexual or physical abuse are common among individuals who self-harm (van der Kolk et al., 1991; Langbehn and Pfohl, 1993; Zlotnick et al., 1996; Pettigrew and Burcham, 1997; Briere and Gil, 1998), and self-harming behaviors are rarely seen after a single, acute trauma (van der Kolk et al., 1991). Self-harm or self-mutilation is a repetitive, compulsive form of self-injury that is distinct from suicide. Individuals who self-injure in this way are not trying to end their life. Instead, self-injury has been described as a coping mechanism to release psychic pain and/or control dissociative episodes. Indeed, Zlotnick and colleagues (1996) found that both dissociative symptoms and alexithymia were independently associated with self-mutilative behavior in female inpatients.

Unfortunately, while self-harming behaviors have been associated with the complex PTSD diagnosis (Zlotnick et al., 1996), no studies have actually examined the prevalence or etiology of self-harm in women with histories of chronic IT who meet DESNOS criteria. Dissociative experiences and self-harming behaviors in women have been linked with borderline personality disorder (Dowson et al., 2000; Sar et al., 2006; Ross, 2007), but a history of IT is not necessary for the development of borderline personality disorder or dissociative phenomena (Zanarini et al., 1999).

A recent comprehensive review by Classen and colleagues (2005) suggests that two out of every three survivors of sexual victimization will be revictimized. CSA,

multiple traumas, and time elapsed since sexual victimization are all risk factors for revictimization. Additionally, according to Classen et al. (2005), women who are revictimized demonstrate increased distress, greater likelihood of psychiatric sequelae and "difficulty in interpersonal relationships, coping, self-representations, and affect regulation, and exhibit greater self-blame and shame". Not surprisingly, many of these phenomena are affiliated with the complex PTSD diagnosis. Since a discussion of the sociopolitical mechanisms underlying sexual and/or physical revictimization of women is beyond the scope of this thesis, the interested reader is referred elsewhere (Noll, 2005).

E. Summary

MDD has been cited as the most common response to IT. The long term prognosis and treatment of depressed women with histories of IT may be complicated by the presence of additional comorbid psychiatric disorders. Therefore, questions regarding IT histories for women seeking treatment for depressive symptoms may provide valuable information in determining other comorbid diagnoses and, subsequently, the course of treatment.

There is still much work to be done around the impact of IT on mental health in women. It is frequently stated that only a small number of women who experience IT go on to develop psychiatric sequelae. This claim is largely unsubstantiated due to a number of methodological issues observed in the literature. Sample selection, sample size, selective examination of specific psychiatric constructs to the exclusion of others, and varying definitions of what constitutes trauma are just a few variables that have led to ambiguity in examining the presence, prevalence and severity of psychiatric illness in the

aftermath of IT. While there are a number of studies that have examined the prevalence of single psychiatric constructs such as major depression or PTSD in select populations (i.e. college samples, women seeking health services), large community samples examining the prevalence and impact of IT on adult mental health are lacking.

The impact of IT severity, duration, and recurrence in the development of specific psychiatric sequelae needs to be explored more fully in future research. Additionally, etiological differences between IT occurring in childhood and adulthood need to be examined since cognitive, behavioral, and physiological differences exist during different phases of the life cycle, potentially contributing to divergent pathways in the type and severity of psychiatric symptoms that may develop. Understanding how and when certain symptoms evolve may provide insight into more effective psychosocial and pharmacological approaches to the treatment of survivors of IT.

II. STRESS-RELATED ILLNESS

Despite widespread, sometimes incorrect use of the term "stress" in present day vocabulary, stress is defined as any threat, real or perceived, to the physiological or psychological well-being of an individual (McEwen, 1999). Within this definition, there is the suggestion that stress may have predictable physical and psychological outcomes. The impact of stressful life events on the development of stress disorders is highly variable between individuals. While it has been noted that the body has two important stress response pathways in the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), the plurality of physiological and behavioral outcomes following acute or chronic stressors is exceptionally broad. A number of

psychiatric disorders, including MDD and PTSD, have been linked to one or both of these stress response pathways.

Early research examining MDD focused on personality traits that may predispose individuals to specific forms of psychiatric symptomatology. The inclusion of the PTSD diagnosis in the DSM-III was a turning point in the acknowledgement that the perception or experience of life-threatening trauma could contribute to the development of psychiatric sequelae. Increasingly, the impact of psychosocial and environmental stressors on the development and maintenance of mental health disorders other than PTSD has been recognized. In particular, the postulated etiology of MDD includes variables such as genetics, predisposing developmental factors, personality traits, cognitive traits, comorbid medical or psychiatric conditions, and psychosocial stressors, among others (Kendler et al., 2002; Iosifescu et al., 2004; Farabaugh et al., 2004; Levinson, 2006; Philibert, 2006). While genetic factors are thought to play a significant role, a continuing theme throughout this research is the dynamic interaction between environmental adversity and depressogenic biological, personality and cognitive traits.

Previous research demonstrated that in individuals who have experienced multiple depressive episodes preceded by life stressful life events, the severity of the stressful event precipitating the depressive episode decreases in subsequent episodes (Perris, 1984; Dolan et al., 1985; Cassano et al., 1989; Brown et al., 1994; Kendler et al., 2000). This led to the "kindling" model explaining the dwindling strength of the relationship between psychosocial stressors and depression as postulated by Post (Post et al., 1991; Post, 2007; Kendler et al., 2000; 2001). A study by Kendler and colleagues (2001) supported these findings but only in individuals at low genetic risk for developing major depression. In

individuals at high genetic risk, major depressive episodes frequently occurred in the absence of major environmental stressors. Thus, as stated by Kendler et al. (2001), "depressive episodes that occur with little provocation may be reached by two pathways: many previous depressive episodes, perhaps driven by multiple adversities, and high genetic risk".

Various internalizing behaviors have been noted for their depressogenic characteristics. Neuroticism, defined as emotional instability or maladjustment, has been cited as a major risk for developing MDD. The interaction between neurotic personality traits and the development of MDD has been demonstrated (Hirschfeld et al., 1989; Kendler et al., 2002), and the impact of neuroticism on illness risk is greater when higher levels of psychosocial adversity are experienced (Kendler et al., 2004). In individuals with low levels of neuroticism, the depressogenic effects of psychosocial adversity are substantially reduced (Kendler et al., 2004). Early-onset anxiety (Breslau et al., 1995), dependency (Widiger and Anderson, 2003), and rumination (Nolen-Hoeksema, 1991; 1994; 1997; 2000) have also been noted for their depressogenic characteristics.

Adverse childhood experiences and family environments play a significant role in the later development of MDD (Reinherz et al., 2003). There are a number of variables that contribute to adverse family environments that have been linked to an increased risk of depression. These include family abuse, conflict, neglect, perceptions of being devalued, substance abuse, larger family size and later birth order (Reinherz et al., 1993). Adverse experiences with key parental and familial figures, especially in early childhood, may result in insecure patterns of attachment later in life, resulting in an elevated risk of depression (Beatson and Taryan, 2003). More severe forms of childhood adversity such

as sexual and physical abuse have been associated with long-term medical and psychiatric conditions such as PTSD, substance abuse, and chronic pain, which have been strongly associated with the comorbid development of depression (Glod, 1993; Rosenberg et al., 1996; Breslau, 2002; Kendall-Tackett, 2002; Kendler et al., 2004; Raphael et al., 2004; Mulvihill, 2005; Lee, 2006).

Gender differences in several predisposing factors thought to contribute to the development of MDD have been observed. Increased levels of neuroticism were observed in females and neuroticism was found to play a significant contributory role in the relationship between being female and MDD (Goodwin and Gotlib, 2004). However, this was not supported by another study (Fanous et al., 2002). Furthermore, personality differences have been shown to be culture-specific (Costa et al., 2001). Women have been demonstrated to have more early onset anxiety (Breslau et al., 1995), dependent personality traits (Widiger and Anderson, 2003), and ruminating personality characteristics (Nolen-Hoeksema et al., 1987; 1997), all variables that have been associated with development of MDD. As discussed earlier, higher rates of IT in both childhood and adulthood have been reported in women and are considered important contributors to the elevated prevalence rate of MDD in women (Campbell, 2002). However, sex differences in the prevalence rate of MDD cannot be accounted for by increased exposure to trauma in women since, with the exception of sexual traumas, men experience trauma more often than women (Breslau et al., 1991; 1998; Kessler et al., 1995). Therefore, sex differences in coping styles, gene-environment interactions, and biological adaptations to stress remain important areas of exploration in the determination

of variables contributing to increased vulnerability of women in the development of MDD.

Kendler and colleagues (2002) developed a developmental model for MDD. Adult female twins (n=1942) were interviewed four times over a nine-year period and the data were used to construct a developmental model to predict the development of major depression in the year before the final interview. Five developmental categories, each with multiple risk factors (noted in brackets) were considered: (1) childhood (genetic risk, disturbed family environment, childhood sexual abuse, and childhood parental loss), (2) early adolescence (neuroticism, self-esteem, and early-onset anxiety and conduct disorder), (3) late adolescence (educational attainment, lifetime traumas, social support, and substance misuse), (4) adulthood (history of divorce and past history of major depression), and (5) the last year (marital problems, difficulties, and stressful life events). Of the 18 risk factors, stressful life events in the preceding year were the most highly predictive of the development of a major depressive episode.

A number of paths (64 paths) leading to a heightened risk of developing MDD were highlighted and demonstrate the intricate interplay between genetic, developmental, and behavioral variables with psychosocial and environmental adversity. This model demonstrated that the risk for developing MDD in women reflected both internal and external variables, as well as the presence of psychosocial adversity. Neuroticism and early-onset anxiety appeared to be the most significant predictors of MDD within the internalizing pathway, while conduct disorder and substance abuse were the most significant variables in the externalizing pathway. The adversity pathway is far more complex, where both childhood and adolescent risk factors impact environmental risk

factors from the preceding year. Early childhood adversities such as disturbed family environment, childhood sexual abuse, and parental loss contribute to the adolescent developmental risk factors of low educational attainment, lifetime trauma and low social support. Preceding year environmental risk factors were influenced by both childhood and adolescent developmental risk factors, resulting in an increased risk of MDD. The authors (Kendler et al., 2002) suggest early life adversities could be re-termed "adversity-interpersonal difficulties" since many early life events involve dysfunctional interpersonal relationships. However, this study selectively examined childhood difficulties that were interpersonal in nature without exploring how other forms of adversity (e.g. natural disaster, poverty, childhood illness) may impact increased susceptibility to MDD later in life.

In summary, Kendler and colleagues (2002) attempted to delineate multi-factorial processes leading to the development of depressive symptoms. This study underlines the importance of environmental adversity, not only in the development of psychiatric states but also in the psychosocial development of the individual starting from childhood. While it is known that specific variables may increase the likelihood of a major depressive episode, further emphasis on the interaction between genetic, behavioral, personality, environmental, and psychosocial variables is necessary in future research.

III. PHYSIOLOGY OF STRESS

A number of biological models have attempted to link acute and chronic stress to the development of mood disorders. The primary focus of much of this work has been the HPA axis where it has been suggested that both genetic predisposition and long-term

sensitization contribute to the development of psychopathology. Both animal and human models have contributed to our understanding of the biological basis of stress disorders. With the evolution of new technologies and molecular techniques, our understanding of the brain is constantly changing and evolving but is still incomplete. In many cases, animal models are used to facilitate our understanding of neurochemical and neuroendocrine processes, allowing much more invasive techniques than can be used in humans. Much of our knowledge regarding the neurobiology of stress has been obtained through manipulations and measurements undertaken using animal models. Debate surrounding the validity of such models is common, particularly regarding many of the stress models that have been developed to study neurochemical changes occurring as a result of acute and/or chronic mild stress paradigms (Willner, 1997; Anisman and Matheson; 2005; Pryce et al., 2005). The result has been an increased understanding of which neurochemicals and neuroanatomical pathways are involved in stress response, but an incomplete understanding of how they may result in psychopathology in humans.

One of the primary reasons biological research has lagged behind psychosocial research in examining major depression and other stress disorders has been our incomplete understanding of the connection between biology and behavior. Some behavioral changes associated with mood disorders such as weight changes, sleep disturbance, psychomotor retardation and anxiety are easier to quantify and can be modeled in animal experiments. Others such as depressed mood, anhedonia, guilt, alexithymia, and other emotional and cognitive states are much more difficult, if not impossible, to model in animals, leading to a knowledge gap in our understanding of the

brain. In the following sections, significant contributions to our understanding of the neurobiology of stress, particularly with regard to the HPA axis, will be reviewed.

A. Early Work

Hans Seyle (1950) was the first to conceptualize the stress response as a non-specific physiological response to demands that are placed on the body. Initial observations of shrunken immune tissues, gastric ulcers, and enlarged adrenal glands following chronic stress led researchers to further investigate the cause of such observations. Seyle's initial formulation of the General Adaptation Syndrome accounted for such observations by separating stress response into 3 distinctive phases: alarm, resistance, and exhaustion. In the alarm phase, also termed the fight or flight phase, physiological responses are diverted from systems like the digestive and immune systems to systems (like skeletal and cardiac muscle and the central and peripheral nervous systems) that are needed to deal with the immediate danger. If the stress continues, the body moves into the resistance phase where it attempts to adapt. As a result of enduring stressors, the body eventually succumbs to the high demands placed on it, resulting in physical and/or psychological maladaptive states and potentially life-threatening illness and disease.

In an attempt to bring together several lines of evidence regarding acute and chronic stress adaptation and health outcomes, the model of allostatic load was developed (McEwan and Stellar, 1993). The principles of allostasis and allostatic load relate to the body's ability to interpret and respond to environmental challenges in a manner that promotes survival and adaptation. McEwen (2000; 2003; 2004) has frequently linked

allostatic load and psychiatric illness to cellular damage within the central nervous system (CNS) involving regions such as the hippocampus, amygdala, and the prefrontal cortex (PFC). When faced with a stressor, the body responds by releasing glucocorticoids and catecholamines, which promote survival and maintenance of homeostasis in the short-term. In the long-term, however, if the stress response is not contained, cellular damage and an acceleration of disease processes may occur. This is termed the allostatic load where the inability of the body to maintain an adaptive homeostatic state translates into chemical imbalance, physiological damage, and subsequent behavioral and physical changes. As stated by McEwen and Stellar (1993), "types of allostatic load include: (1) frequent activation of allostatic systems, (2) failure to shut off allostatic activity after stress, and (3) inadequate response of allostatic systems, leading to elevated activity of other, normally counter-regulated allostatic systems after stress".

Since this initial conceptualization of the stress response, our knowledge of neurochemistry, neuroendocrinology, and neuroanatomy has increased dramatically and continues to evolve. While popular culture has incorrectly redefined stress as primarily psychological or emotional in nature, stressors have both psychological and physiological components. Systems responsible for the initiation of stress-related physiological responses such as increased cardiac output and respiration, increased blood pressure, and increased catabolism are linked to areas of the brain thought to be responsible for emotion, anxiety-related behaviors, attention and storage of memories. Given the wide range of functions potentially affected by stress, it is not then surprising that a variety of diseases have been associated with stress. Cardiac disease, obesity, type II diabetes, some forms of psychiatric illness such as MDD and PTSD, and somatic complaints, among

others, have all been linked to stress (Sapolsky, 2004). In many cases, stress-related disorders occur together, reflective of the wide range of functions that are affected by stress.

The genome plays an important role in shaping the development and general functioning of the CNS, but it is environmental interaction and experience that determine an individual's behavior (Vermetten and Bremner, 2002). Past experience shapes the sensitivity and responsivity of the stress response system, leading to both physiological and behavioral responses that may either be adaptive or maladaptive in nature. As stated by Vermetten and Bremner (2002), "central aspects of the stress response system involve perception of a stressor or fear-producing stimulus, processing, and transduction of this information into neurohormonal, neurobiological, and behavioral responses." A key tenet of biological psychiatric research is the assumption that maladaptive behavioral features will exist in parallel with maladaptive biological mechanisms or pathways. Thus, in terms of stress-related disorders, physiological disruptions at the perception, processing, or transduction phases may potentially result in symptoms associated with specific psychiatric disorders.

The two primary stress response systems are the HPA axis and the central sympathetic/adrenomedullary system, which influence both body organs and other neural pathways during exposure to adverse stimuli (Tsigos and Chrousos, 2002). The sympathetic noradrenergic stress response is considered fast-acting but quickly-depleting, while the HPA axis cascade is slower-acting but longer-lasting in the face of adverse stimuli (Vermetten and Bremner, 2002). While corticotrophin releasing hormone (CRH), glucocorticoids and noradrenaline are directly associated with stress response, other

neurotransmitters such as serotonin, γ-aminobutyric acid (GABA), dopamine, glutamate, β-endorphin (β-END), and numerous other neuropeptides and neurohormones are thought to play neuromodulary roles. The circuitry and pathways involved in the physiology of stress are also well reviewed elsewhere (Vermetten and Bremner, 2002; McEwen, 2002; Charney, 2003).

B. HPA Axis

Over the past four decades, the field of neuroendocrinology has been central to our increasing understanding of the connection between stress and the development of maladaptive states. As early as the 1960's, researchers found changes in plasma cortisol concentrations in individuals due to chronic stress or during periods of heightened stress (Friedman et al., 1963). Since that time, our understanding of the HPA axis cascade has evolved considerably.

Vale (1981) isolated a 41 amino acid peptide named CRH which stimulated the release of both adrenocorticotrophin hormone (ACTH) and β-END. Until 1981, it was thought that arginine vasopressin (AVP) was the principal hypothalamic stimulus to the pituitary-adrenal axis (Scott and Dinan, 1998). It is now known that AVP is an important synergistic factor with CRH in the release of ACTH. Alone, AVP has limited ACTH secretegogue activity but when administered with CRH, the ACTH releasing potential far exceeds that when either peptide is administered alone (Gillies et al., 1982; Rivier and Vale, 1983; Lamberts et al., 1984; Antoni, 1986). CRH and AVP are co-localized in the parvocellular neurons of the paraventricular nuclei (PVN) in the hypothalamus (Whitnall et al., 1987). During periods of quiescence, CRH and AVP are secreted into the median

eminence in a circadian, pulsatile manner with a frequency of about 2-3 bursts per hour (Engler et al., 1989) with higher amplitude pulses in the early morning hours (Horrocks et al., 1990). Following adverse or stressful stimuli, the amplitude and frequency of CRH and AVP pulses increase markedly, initiating the release of ACTH from the anterior pituitary.

ACTH is released from the anterior pituitary following CRH_1 and/or $vasopressin_{1b}$ (V_{1b}; primary AVP receptor in the anterior pituitary) receptor stimulation (Scott and Dinan, 1998). After entering the bloodstream, ACTH stimulates the synthesis and release of cortisol from the adrenal cortex by interacting with melanocortin-2 receptors on adrenocortical cells. Basal release of both ACTH and cortisol is pulsatile and follows a circadian rhythm that is sensitive to sleep, light, stress, and illness (Yehuda et al., 1994). During early waking hours, levels of cortisol are at their highest with levels declining as the day progresses (Keller-Wood and Dallman, 1984; Cascio et al., 1987).

Once in the bloodstream, cortisol participates in a number of physiological processes that enable the body to cope with both acute and chronic stressors. Cortisol stimulates both gluconeogenesis and the release of fatty acids to ensure glucose for energy utilization during an acute stressor. For more chronic stressors, cortisol inhibits growth, reproductive, and immunological processes. This allows physiological resources and energy stores to be diverted into processes that facilitate coping with chronic stressors. However, long-term alterations in glucocorticoid-related functions are thought to play a role in various disease states such as hypertension, obesity, type II diabetes, and affective disorders (Whitworth et al., 2005; Balon, 2006; Keller, 2006; Pasquali et al.,

2006). The role of cortisol in the development and pathophysiology of these disease states is currently unknown.

Cortisol is free to cross the blood-brain barrier where it participates in the homeostatic regulation of the HPA axis. Feedback regulation of the HPA axis by glucocorticoids is maintained by two distinct intracellular receptors called the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR) (Reul and de Kloet, 1985). The MR has a higher affinity for cortisol than the GR and is thus thought to play a more substantial role in the regulation of basal and circadian fluctuations of cortisol. During periods of stress and circadian peak when glucocorticoid levels are high, feedback regulation by GRs is thought to become significant. Both types of receptor are distributed throughout the brain in regions thought to be important in the initiation, maintenance, and termination of stress responses. These include the hippocampus, hypothalamus, pituitary, amygdala, and PFC (Herman et al., 2005).

C. CRH

C.1. Introduction

Vale and colleagues (1981) first hypothesized that CRH was a key neuropeptide in the mediation and integration of "endocrine, visceral and behavioral responses to stress". Since its initial discovery, both preclinical and clinical research have confirmed this hypothesis and have enhanced our understanding of the role of CRH in fear and anxiety responses. CRH has been implicated in numerous mood and anxiety-like behaviors and has been shown to impact arousal, alertness, attention, appetite, psychomotor behavior, and immune response (Holsboer, 2001). Initial research

exclusively examined the CRH in the context of the HPA axis signaling cascade. It is now known that CRH also has important extrahypothalamic functions in the modulation of stress and anxiety responses in addition to its role as a secretagogue of ACTH. Neural circuits outside of the hypothalamus are responsible for many of the behavioral manifestations of CRH and its related receptors (Owens and Nemeroff, 1991). The localization, pharmacology, and role of CRH in anxiety and stress responses will be discussed in the following sections.

C.2. Synthesis, Location and Pharmacology of CRH

Hypothalamic CRH

In the context of the HPA axis, CRH-containing cell bodies are contained within the parvocellular PVN of the hypothalamus and have projections which terminate in the external zone of the median eminence (Sawchenko et al., 1984; de Goeji et al., 1991). From the median eminence, CRH is released into portal circulation where it enters the anterior pituitary and acts on pituitary corticotrophs which release ACTH. Subsequently, ACTH enters the bloodstream in the periphery to stimulate the release of cortisol from the adrenal cortex.

Multiple lines of transgenic mice have been bred to enhance our understanding of the endocrine and behavioral consequences of changes in CRH release, neurotransmission and responsivity. Transgenic mice overexpressing CRH demonstrate increased grooming behaviors and decreased spontaneous movements in a familiar environment as well as decreased locomotor activity in novel environments demonstrative of increased anxiety in these mice (Stenzel-Poore et al., 1994; Heinrichs et

al., 1997). Furthermore, these mice developed increased production of ACTH and cortisol and subsequently, Cushing's-like symptoms, as well as desensitization of the HPA axis in response to stress (Stenzel-Poore et al., 1992). Conversely, in CRH knock-out mice (CRH not expressed in these mice) there was a blunting of basal and stress-induced cortisol levels (Muglia et al., 1995; Dunn et al., 1999), as well as delayed and reduced adrenaline and noradrenaline levels in response to stress (Jeong et al., 2000). Unlike transgenic mice overexpressing CRH, CRH knock-out mice had normal behavioral responses to stress (Weninger et al., 1999; Dunn et al., 1999).

CRH has a high affinity for CRH binding protein (CRH-BP), which is found predominantly in the liver, blood, pituitary, and brain (Potter et al., 1991; Potter et al., 1992; Cortwright et al., 1995). It has been demonstrated that the binding of CRH to CRH-BP quickly inactivates CRH, which serves as a mechanism to regulate its endocrine and neuromodulatory functions (Lowry et al., 1996). Overexpression of CRH-BP had little effect on basal and stress-induced ACTH and cortisol levels in two different transgenic mouse models (Lovejoy et al., 1998; Burrows et al., 1998). However, transgenic mice overexpressing CRH-BP were found to have increased CRH and AVP levels, likely as a compensatory mechanism. CRH-BP knockout mice were also found to have normal basal and stress-stimulated ACTH and cortisol levels (Smith et al., 1998). Knock-out mice also demonstrated an increase in anxiety-like behaviors, which likely occurs as a result of increased CRH availability due to the absent buffering normally provided by CRH-BP.

Two families of CRH receptors exist in the body: CRH_1 and CRH_2. These receptors appear to exert opposing effects, with the CRH_1 subtype mediating anxiogenic and stress-invoked behavioral and physiological responses (Timpl et al., 1998) and the

CRH_2 subtype mediating anxiolytic responses (Hashimoto et al., 2000). CRH_1 receptors are distributed throughout the pituitary, hippocampus, amygdala, bed nucleus of the stria terminalis (BNST), cerebral cortex, cerebellum, olfactory bulb, and medial septum (Potter et al., 1994), while CRH_2 receptors are mostly observed in peripheral tissues such as the heart, lungs, skeletal muscle and gastrointestinal tract but are also found in the hypothalamus and lateral septum (Lovenberg et al., 1995; Perrin et al., 1995; Stenzel et al., 1995). A review by Aguilera and colleagues (2004) provides a more complete summary of CRH receptor distribution. Both CRH_1 and CRH_2 are G-protein-coupled to the adenylyl cyclase/cAMP signaling system (Aguilera et al., 1983). Much of our understanding of the morphology of CRH receptors has been elucidated using animal models (Aguilera et al., 2004; Bale and Vale, 2004)

Transgenic mice have also been used to further our understanding of the functions of CRH_1 and CRH_2 receptors. While overexpression models have not been developed for CRH receptor subtypes, researchers have bred lines of knock-out mice. CRH_1 receptor knock-out mice show normal basal levels of ACTH and cortisol, but blunted responses to restraint stress compared to wild-type mice (Smith et al., 1998; Timpl et al., 1998). These mice also show reduced anxiety levels. Conversely, mice lacking CRH_2 receptors showed increased anxiety-like behaviors (Bale et al., 2000). Furthermore, CRH_2 receptor knock-out mice had normal basal ACTH and cortisol levels, but rapid and elevated ACTH and cortisol responses to restraint stress (Bale et al., 2000, Coste et al., 2000). These findings suggest that while pituitary CRH_1 receptors are necessary for appropriate regulation of the HPA axis, CRH_2 receptors may serve to modulate HPA axis responses to stress.

CRH receptors in the pituitary are markedly affected by alterations in HPA axis activity (Aguilera, 1994). Hypersecretion of CRH observed in many rodent chronic stress models leads to CRH_1 receptor downregulation and desensitization. However, as reviewed by Aguilera and colleagues (1994; 2004), there is poor correlation between the number of CRH receptors in the anterior pituitary and the release of ACTH, since full ACTH release can be achieved without full receptor occupancy.

Extrahypothalamic CRH

CRH-containing neurons modulate a number of diverse brain structures and neurotransmitter systems outside of the hypothalamus. Cell bodies containing CRH are also distributed in regions such as the amygdala, BNST, cortex, lateral hypothalamus, parabrachial nucleus, ventrolateral medulla, and Barrington's nucleus (Valentino and Van Bockstaele, 2002). Further, CRH projections have been found to densely innervate the locus coeruleus (LC) and the dorsal raphe nucleus which are primary sites of noradrenergic and serotonergic cell bodies respectively (Ruggiero et al., 1999; Kirby et al., 2000). Based on this anatomical evidence, CRH is situated in several structures within the CNS known to regulate arousal, autonomic behavior and fear processes, as well as interacting with biogenic amine structures implicated in the regulation of mood and anxiety. Furthermore, rodent models have demonstrated extrahypothalamic CRH can mediate behaviors such as decreased sleep, anorexia, decreased locomotor activity, inhibition of sexual receptivity, decreased gastrointestinal motility, increased startle, and decreased exploratory behavior in a novel environment (Dunn and Berridge, 1990; Koob et al., 1993; Young and Liberzon, 2002).

It has been hypothesized that hypothalamic CRH release occurs in response to physiological stress, while CRH release from the central nucleus of the amygdala occurs in response to fear-related behaviors (Makino et al., 1999) and emotionally significant stimuli (Merali et al., 2003). The central nucleus of the amygdala has long been thought to play an important role in fear responses and the development of emotional memory. A number of neural networks and brain structures known to be involved in stress responses receive input from the amygdala. These include the lateral hypothalamus which mediates sympathetic activation and the PVN which activates the HPA cascade. Also receiving input from the amygdala during stress are the ventral tegmental area, dorsolateral tegmental nucleus and LC which initiate behavioral arousal and increased vigilance, and the periaqueductal gray (PAG), which modulates escape, fighting, freezing, and vocalization (Coupland, 2000; Van Bockstaele et al., 2001). Thus, activation of the amygdala has the potential to evoke stress responses via a number of output pathways that mediate fear behaviors. Given the distribution and localization of CRH and its related receptors in regions throughout the brain involved in sensory processing and association, anxiety and fear responses, cognition, memory, emotion and mood, CRH is poised to play a dominant and comprehensive role in the coordination of stress responses.

Using a rodent model, Makino and colleagues (1999) observed that following a psychological stressor, the activation of the amygdalar CRH system can occur without robust activation of the hypothalamic CRH system. Comparatively, the hypothalamus acts primarily through the pituitary in releasing endocrine factors that regulate peripheral functions while the amygdala is better suited to affect changes in the CNS through its vast interconnectivity to areas of the brain involved in autonomic, endocrine, behavioral,

and cognitive functions. Many stressors bear both physiological and psychological characteristics. The limbic system can activate the HPA axis in the absence of physiological stressors by indirect means (e.g. excitatory noradrenergic inputs from the LC; Herman et al., 2003). Thus, while the limbic stress system may only be responsive to pathways involving higher order processing (Herman and Cullinan, 1997), the HPA axis may still be activated as a result of psychological stressors. Over-activation of the limbic system in the face of psychological distress may thus play a role in the development of HPA disturbances observed in stress disorders.

Regulation of the LC and dorsal raphe nucleus by CRH projections from the amygdala has particular importance in the pathophysiology of mood and anxiety disorders. Serotonin (5-hydroxytryptamine; 5-HT) and/or noradrenaline are targeted by almost all contemporary antidepressant and anti-anxiety medications. The mechanisms by which medications like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and serotonin-noradrenaline reuptake inhibitors (SNRIs), among others, relieve depression and anxiety symptoms remain to be fully elucidated following decades of research. Further exploration of the means by which CRH dysregulation can affect neuromodulation of these two neurotransmitter systems in normal and disordered affective and anxiety responses is necessary (Koob, 1999; Charney, 2004; Risbrough and Stein, 2006). Data regarding the key role of CRH in depressive symptoms has led to the development of CRH antagonists as putative antidepressants (Hauger et al., 2006).

C.3. Methodological Considerations

CRH is normally measured in either plasma or cerebrospinal fluid (CSF) using custom or commercial ^{125}I radioisotope kits (Phoenix Peptides, Bachem). While these kits usually have low cross-reactivity with other neuropeptides, they require an advanced level of laboratory resources and expertise to work with ^{125}I radioisotopes. Commercial enzyme-linked immunoassay (ELISA) kits and systems are also available (Phoenix Peptides). However, the sensitivities of such kits are inadequate to measure CRH in human biological fluids.

Perhaps a more important issue is the decision to use plasma or CSF to measure CRH in clinical populations. Most studies that examine CRH levels in clinical psychiatric populations have used CSF rather than plasma. Doing so requires advanced medical expertise to perform lumbar punctures on participants, which are often very painful and increasingly call into question ethical standards for the treatment of research participants. Presently, there is no firm evidence to suggest it is beneficial to use CSF rather than plasma when measuring CRH. However, it has been suggested that peripheral sources of CRH do exist (Mastorakos et al., 2006; Kalantaridou et al., 2007) and thus changes in peripheral release of CRH may confound data seeking to assess differences in CNS CRH. Whether measured in human plasma or CSF, there is presently no way to differentiate between hypothalamic and extrahypothalamic CRH. This is problematic since the endocrine and neuromodulatory roles of CRH are very different and the sites of CRH dysregulation in the CNS must be identified to further our understanding of stress disorders. Using animals, direct measurement of CRH levels from specific brain regions is possible. In humans, however, we are presently limited to the use of CSF or plasma,

which reflect a balance between CRH release, enzymatic degradation and clearance (Kaschow et al., 2001). The development of radiotracers selective for CRH receptors may allow researchers to examine CRH neurotransmission in the CNS more selectively using the neuroimaging technique positron emission tomography (PET).

D. AVP

D.1. Introduction

AVP was first isolated, identified and synthesized in 1954 by du Vigneaud and colleagues (du Vigneaud et al., 1954). Since its initial discovery, several functional roles of AVP have been established. First and foremost, AVP is a powerful antidiurectic and is released from the posterior pituitary in response to increasing plasma osmolality and hypovolemia, as well as hypotension and hypoglycemia (Dunn et al., 1973; Laszlo et al., 1991). Second, the role of AVP as a co-secretagogue with CRH in stimulating the release of ACTH in the HPA axis signaling cascade has been well established. As such, animal models and studies in healthy and clinical populations have further established a role for AVP in the regulation of physiological and psychological stressors and anxiety states. The physiology of AVP in the regulation of stress response will be explored in the following sections.

D.2. Synthesis, Location and Pharmacology of AVP

AVP-containing cell bodies are localized within the hypothalamus and are subdivided within specific areas of the hypothalamus on the basis of functional role. Magnocellular neurons containing AVP have cell bodies localized within the supraoptic

nucleus and PVN and nerve endings in the external zone of the median eminence. Osmotic stressors, such as increasing plasma osmolarity, hypovolemia, and hypotension cause AVP vesicles to be released from magnocellular neurons into the median eminence, where they are transported into the posterior pituitary and subsequently released into peripheral circulation (Holmes et al., 1986). Parvicellular neurons have cell bodies localized primarily within the PVN and AVP is secreted into pituitary portal circulation via nerve endings projecting to the median eminence (de Goeji et al., 1991). These cell bodies are localized within the dorsomedial parvicellular subdivision of the PVN and release both CRH and AVP. Once AVP enters portal circulation, it is transported to the anterior pituitary, where it acts on pituitary corticotrophs to release ACTH. Three populations of pituitary corticotrophs have been identified: (1) CRH-sensitive corticotrophs, (2) AVP-sensitive corticotrophs, and (3) CRH/AVP-sensitive corticotrophs (Jia et al., 1991). AVP is also found in the BNST, amygdala, dentate gyrus, nucleus accumbens, dorsomedial suprachiasmatic nucleus, cerebellum, intermediate lobe of the pituitary, and the septal region (Gerstberger et al., 1989).

With regard to the relative proportions of CRH- and AVP-containing neurons in the parvicellular subdivision of the PVN, differences between rodents and humans have been noted. In non-stressed rats, approximately 50% of CRH-containing neurons of parvicellular neurons also co-express AVP (Whitnall et al., 1987). In humans, there is evidence to suggest that all CRH neurons in the parvicellular neurons of the PVN contain AVP (Mouri et al., 1993). These species differences are important, since rodent models have been used to show increases in the proportion of AVP-secreting neurons following chronic stress and will be discussed in later sections. They are noted here to point out that

rodent models may not be an adequate reflection of stress-induced changes in human brain. If all human CRH-containing neurons in parvicellular neurons of the PVN also contain AVP, then the proportion of AVP-expressing neurons cannot increase as a result of chronic stress. However, increases in AVP vesicle and concentration may occur (De Goeji et al., 1992a, b).

In the anterior pituitary, AVP interacts with V_{1b} receptors on corticotrophs to stimulate the release of ACTH through the phosphatidylinositol second messenger system (Jard et al., 1986; Lolait et al., 1995). These receptors are also found in other brain regions as well as in the heart, lungs, breast, and kidneys. Other receptors, which are less relevant for this discussion, include the V_{1a} receptor which is found on blood vessels and in some brain regions and V_2 receptors, which are found in principal cells of the renal collecting system in the kidney (De Wied et al., 1991).

While it has been repeatedly established that the synergism between AVP and CRH in stimulating the release of ACTH is far in excess of either peptide alone (Gillies et al., 1982; Rivier and Vale, 1983; Lamberts et al., 1984; Antoni, 1993), the potency of AVP in the absence of CRH is debatable. One study found CRH to be the more potent ACTH secretagogue (Salata et al., 1988), while another study found AVP and CRH to be equally effective alone (Murakami et al., 1984). A mouse model using CRH_1 receptor deficient mice found that AVP can act as a compensatory mechanism to overcome impairments in CRH signaling and maintain HPA activity (Turnbull et al., 1999; Muller et al., 2000). Thus, while many researchers believe that CRH is the primary regulator of the HPA axis, with AVP adding a synergistic and/or compensatory effect, the role of AVP in maintaining the HPA axis may be underappreciated.

The mechanism by which AVP and CRH synergistically stimulate the release of ACTH is not well understood. A selective V_{1b} receptor antagonist (SSR149415) has been developed. This compound prevents the rise in ACTH caused by AVP and possesses antidepressant and anxiolytic properties (Serradeil-Le Gal et al., 2002; Greibel et al., 2002). Tanoue and colleagues (2004) found that CRH induced rises in ACTH in V_{1b} receptor-deficient mice were not significantly different than those observed in mice that were not deficient in V_{1b} receptors. Equivocal data exist on the impact of decreased V_{1b} receptor density on basal ACTH levels, with some researchers finding V_{1b} receptor-deficient mice having lower basal levels of ACTH than wild type mice (Tanoue et al., 2004), while others finding similar basal ACTH levels (Lolait et al., 2007). This is in contrast to a study that found similar basal levels of ACTH in CRH_1 receptor-deficient mice when compared to wild type controls (Timpl et al., 1998). Further, the increase in ACTH in V_{1b} receptor-positive mice was significantly higher than that observed in V_{1b}-deficient mice following a forced swim test and in another study using chronic restraint stress (Lolait et al., 2007). Finally, in CRH_1 receptor-deficient mice, an increase in the activity of the vasopressinergic system has been noted with increases in basal plasma AVP, AVP mRNA in the PVN, and increased AVP in the median eminence (Muller et al., 2000). Therefore, the physiological contributions of AVP and the V_{1b} receptor on pituitary corticotrophs may be particularly important during periods of stress but also play an important role in the regulation of basal ACTH levels.

Further studies examining changes in CRH_1 and V_{1b} receptor numbers occurring as a result of chronic alterations in CRH and AVP have also demonstrated syngerism between the two peptides. Minipump infusion of CRH into the pituitary resulted in

decreased numbers of CRH_1 receptors, which was further reduced by simultaneous infusion of AVP (Tizabi et al., 1992). Elevations in CRH and AVP brought about by chronic stress have also been found to decrease the number of CRH_1 receptors in the pituitary (De Goeji et al., 1992; Tizabi et al., 1992). Conversely, repeated immobilization stress resulted in an increase in V_{1b} receptor mRNA in the pituitary, reflective of potential V_{1b} receptor upregulation occurring as a result of chronic stress (Rabadan-Diehl et al., 1995).

D.3. AVP and Stress Models

It has long been appreciated that CRH and AVP are released in response to stress and play primary roles in the initiation of the HPA axis. Animal stress models have suggested that CRH and AVP may be released in varying proportions dependent upon the type and duration of the stressor (Romero and Sapolsky, 1996). Scott and Dinan (1998) summarized the role of AVP in ACTH release as a function of the animal paradigm used. Using rodent models of acute stress, AVP played a role in the release of ACTH during frustration (Romero et al., 1995), submission (Romero et al., 1995), immobilization stress (Negro-Vilar and Saavedra, 1980; Bartanusz et al., 1993a,b; Bartanusz et al., 1994), and footshock (Knepel et al., 1985; Romero and Sapolsky, 1996). AVP appeared to have no role in a social isolation model and CRH was the primary ACTH secretagogue, while in footshock stress, AVP was the primary ACTH secretagogue (Romero and Sapolsky, 1996). Studies examining novelty stress in rodents have been inconclusive (Lutz-Bucher and Koch, 1983; Priou et al., 1993; Romero and Sapolsky, 1996). Using human stress

models, plasma AVP levels increase during social isolation and confinement (Maillet et al., 1993) and during exposure to psychological stressors (Meyerhoff et al., 1990).

AVP release has also been examined in animal models of chronic stress. Chronic psychosocial (De Goeji et al., 1992) and immobilization stress (Hauger et al., 1990) led to increased synthesis of AVP in parvicellular neurons of the PVN as well as increased presence of AVP in nerve terminals in the median eminence. Further evidence suggests that during chronic stress, the hypothalamic AVP/CRH signal may shift in favor of AVP, as demonstrated in psychosocial and immobilization stress models (Bertini and Kiss, 1991; Whitnall, 1989; Scott and Dinan, 1998). Finally, using rodent stress models, an increased proportion of parvicellular neurons co-expressing both CRH and AVP have been observed. As described earlier, this finding may not be relevant for humans (Mouri et al., 1993).

D.4. Methodological Considerations

There are a number of good commercial kits available to measure AVP in plasma using ELISA with low-cross reactivity and reasonable sensitivity (American Research Products Inc, Assay Designs/Stressgen Bioreagents, Biomeda Corporation, RnD Systems). The primary issue in the measurement of AVP involves the validity of using biological fluids such as plasma in the periphery to infer changes in AVP levels occurring in the anterior pituitary within the context of the HPA axis.

Plotsky (1991) has suggested that peripheral AVP levels may be an order of magnitude lower than those found in portal circulation within the pituitary. However, AVP is also released into peripheral circulation via the posterior pituitary in response to

osmotic stressors such as increasing plasma osmolarity, hypovolemia, and hypotension. While AVP from parvicellular hypothalamic neurons acts primarily in the anterior pituitary by regulating the HPA axis, that released by magnocellular hypothalamic neurons into the posterior pituitary acts on the kidneys, blood vessels and other sites within the periphery and its release is stimulated by very different triggers. Unfortunately, there is no evidence to define the relative contributions of parvicellular and magnocellular sources of AVP in the periphery. Therefore, when conducting peripheral measurements of AVP in plasma as part of studies of the HPA axis, it may be important to maintain constant fluid volumes in participants as well as monitor blood pressure to lower the risk of changing AVP levels occurring as a result of osmotic stressors. Doing so will reduce variation in the amount of AVP released from the posterior pituitary and increase the likelihood that changes in plasma AVP levels that occur during challenges of the HPA axis can be directly attributable to that released into the anterior pituitary.

E. Regulation of the HPA Axis

The HPA axis plays a key role in adaptation to internal and external challenges and attempts to maintain homeostatic balance within the body. Doing so requires both intrinsic and extrinsic mechanisms of control over the HPA axis to ensure an optimal level of functioning in response to homeostatic challenges. Multiple brain regions are directly and indirectly interconnected with the HPA axis and are responsible for the activation or inhibition of the hypothalamic PVN in the face of perceived challenges to homeostasis. Once activated, appropriate feedback mechanisms are also in place to ensure HPA axis functioning is returned to basal levels after the challenge has ended.

Tight regulation of the HPA axis is crucial, and imbalances associated with this cascade have been associated with numerous disease processes. While a complete review of this literature is beyond the scope of this thesis, interested readers are referred to key reviews around regulation of the HPA axis (Herman et al., 1996; 2003; 2005). This literature will be summarized in the following paragraphs.

E.1. Negative Feedback by Glucocorticoids

Since glucocorticoids induce genomic actions, regulation of the cortisol secretion and the HPA axis cascade is essential. In humans, cortisol release has a distinct circadian rhythm regulated by the suprachiasmatic nucleus, with levels highest in the morning (Keller-Wood and Dallman, 1984; Cascio et al., 1987). Secretion of glucocorticoids in response to disruptions in homeostasis is tightly regulated to prevent prolonged elevations that may induce cellular damage or dysfunction. Cortisol is free to cross cellular membranes, where it enters the nucleus and modulates gene transcription by binding with gene transcription factors or gene response elements (Pearce and Yamamoto, 1993; McKay and Cidlowski, 1998). Glucocorticoid receptors are responsible for mediating the biological activity of cortisol and for providing negative feedback on the HPA axis. Negative feedback is induced when CRH and/or AVP release from neurons in hypothalamic PVN is prevented and the HPA axis cascade is thus blocked. MRs are thought to maintain basal HPA axis tone, while GRs seem to be more important for the regulation of stress responses (Ratka et al., 1989; Dallman et al., 1989; De Kloet et al., 1998).

Chronic stress has been shown to induce both habituation and facilitation of the HPA axis (Herman et al., 2005). Habituation occurs when a specific stressor is applied repeatedly and the glucocorticoid response diminishes in response to the stressor (Cole et al., 2000). Conversely, in facilitation, exposure of chronically stressed animals to a novel stimulus leads to elevated glucocorticoid response compared to non-stressed controls (Akana et al., 1992). Further, in human subjects, elevated cortisol release in response to psychosocial challenge has been noted in survivors of IT with MDD (Heim et al., 2000) or PTSD (Elzinga et al., 2003; Bremner et al., 2003). Thus, the mechanisms by which facilitation occurs may have important implications in the pathophysiology of stress disorders.

In addition to feedback regulation by glucocorticoids, several structures within the CNS are known to be involved in the integration of HPA axis activity. Signals regarding perturbations in the internal environment are predominantly relayed to the hypothalamic PVN by brain stem pathways. The NTS and ventrolateral medulla appear to relay signals involving cardiovascular, respiratory, or visceral stimuli to the PVN (Swanson and Sawchenko, 1983; Cunningham and Sawchenko, 1988; Herman et al., 2005). Infection and/or toxins in the periphery are also known to stimulate the HPA axis via ascending brain stem afferents (Ericsson et al., 1994; 1997) or by stimulating local synthesis of prostaglandins (Rivest, 2001) and/or nitric oxide (Rivier, 2001; Herman et al., 2005). Ascending projections from autonomic centers of the brain to the PVN are usually peptidergic (enkephalin, NPY, neurotensin, dynorphins) or catecholaminergic in nature (Palkovits, 1999).

Physiological and psychological stimuli invoked by changes in the external environment are far more complex and require the recruitment and integration of signals involving sensory, cognitive, emotional, memory, fear, and defensive processes. Glucocorticoid receptors have been identified in the hippocampus, amygdala, medial PFC, BNST, LC, and raphe nucleus and each of these areas has been found to exert control over the HPA axis. While brainstem nerve populations innervate PVN nuclei directly, the BNST appears to coordinate all stress-regulatory signals from regions such as the hippocampus, amygdala, medial PFC and other regions involved in stress responding to the PVN (Canteras et al., 1995; Crane et al., 2003; Herman et al., 2005). Further, while the amygdala appears to have a predominantly stimulatory effect on the HPA, the regulatory impact of other regions such as the hippocampus and medial PFC appears to be complex and stressor-dependent (Herman et al., 2003; Herman et al., 2005).

Not surprisingly, many of the brain structures that have been implicated in the regulation of the HPA axis have also been implicated in stress disorders such as MDD, PTSD, and other anxiety disorders, among others. The intricate interconnectivity between these structures highlights the importance of further preclinical and clinical research to ascertain the connection between dysregulation within the CNS and psychiatric symptoms occurring as a result of stress. Dysregulation within one area of the limbic system has the potential to cause dysfunction in multiple others due to the vast interconnectivity within this system. The primary issue is identifying which forms of dysregulation contribute to psychiatric symptoms associated with exposure to acute or chronic stress and which are simply surrogate markers of dysfunction within other systems.

IV. HPA AXIS AND MDD

As one of the body's major stress response systems, the integrity of the HPA axis has been repeatedly examined in stress-related psychiatric illness. Initial studies examined plasma and urinary cortisol levels in individuals with MDD. This research later expanded to include the examination of other regulatory peptides such as CRH, AVP, ACTH, and β-END as well as changes in glucocorticoid receptor density and decreased negative feedback on the HPA axis in depressed individuals. Over the last 50 years, both preclinical and clinical studies have contributed to a huge body of evidence that identifies HPA axis dysregulation in many individuals with MDD. While HPA axis dysregulation has not been consistently observed in all individuals with MDD, it has been widely accepted as a dysregulated pathway in the pathophysiology of MDD.

Early research involving the HPA axis and MDD has given way to the role of the HPA in stress-related psychiatric illness in general. In particular, HPA axis dysregulation has also been observed in PTSD. Unlike MDD, discrepant findings have been observed involving the HPA and PTSD. This may be attributed to the plurality of behavioral responses to severe stressors. As discussed earlier, female survivors of IT frequently have symptoms of both MDD and PTSD.

A. Cortisol Hypersecretion in Depression

Initial indications that HPA axis functioning was compromised in depressed individuals was discovered 50 years ago when elevated basal plasma cortisol levels were observed in patients with MDD (Gibbons and McHugh, 1962; Gibbons, 1964). Further evidence that HPA axis functioning may be compromised in individuals with MDD came

from studies examining Cushing's disease. Individuals with Cushing's disease often exhibit severe depression as well as elevated production and secretion of glucocorticoids (Brown et al., 2004; van Rossum and Lamberts, 2006). Early research examining basal cortisol levels in MDD and Cushing's Disease contributed to the modern stress-diathesis model of depression, whereby dysregulation within the HPA axis is explicitly linked to the etiology of depression.

Since the initial discovery that cortisol levels may be elevated in individuals with MDD, hundreds of studies have been carried out attempting to correlate baseline cortisol levels with mood. Although basal cortisol hypersecretion has been generally accepted as a clinical observation in MDD (Steckler et al., 1999; Plotsky et al., 1998; Nemeroff and Vale, 2005), not all studies support these findings (Peeters et al., 2004; Burke et al., 2005). In response to the variability observed in studies examining baseline levels of cortisol in individuals with MDD, researchers started to examine changes in plasma cortisol levels resulting from pharmacological challenge. Cortisol levels obtained in the context of neuroendocrine challenges are often more informative than baseline measurements, due to intra- and inter-individual variability in basal cortisol levels. One such challenge is the dexamethasone suppression test (DST), where a low dose of a synthetic glucocorticoid, dexamethasone (DEX), ranging from 0.25-1.5mg, was used frequently in research examining the integrity of the HPA axis in depressed individuals. DEX suppresses ACTH production in the anterior pituitary corticotrophs and subsequently leads to the suppression of cortisol release from the adrenal cortex for 24-48 hours. Non-suppression of cortisol release by DEX has been demonstrated in some, but not all, individuals with MDD (Arana et al., 1985; Braddock et al., 1986; Ribeiro et al.,

1993; Rush et al., 1997). It has been suggested that cortisol non-suppression by DEX in individuals with MDD is a marker of impaired feedback regulation and HPA axis hyperactivity. Only about 44% of depressed individuals demonstrate DEX non-suppression, disqualifying the DST as a diagnostic screening test (Arana et al., 1985; Christensen and Kessing, 2001). However, a meta-analysis by Nelson and Davis (1997) revealed that DEX non-suppression status was more commonly found in individuals with MDD with psychotic features than in those with MDD alone. Elevated basal cortisol levels and/or failure of DEX to reduce elevated cortisol levels has been observed in up to 2/3 of depressed individuals (Carroll et al., 1981; Gold et al., 1988; Chrousos and Gold, 1992; Holsboer and Barden, 1996; Nemeroff, 1996; 1998).

Attempts have been made to correlate clinical relationships between the suppressor and non-suppressor status of depressed individuals. These attempts have been largely unsuccessful, with no relationships identified between the type, duration, or severity of depressive symptoms. However, it has been demonstrated that in those individuals who remain DEX non-suppressors following successful treatment of depressive symptoms, the risk of relapse is substantially higher (Ribeiro et al., 1993).

Following the discovery of CRH as a hypothalamic releasing hormone for ACTH, synthetic CRH (1μg/kg) was used to challenge the HPA axis in depressed individuals. While healthy controls show elevated ACTH and cortisol release following CRH challenge, depressed individuals who are non-suppressors following the DST had blunted ACTH release and normal cortisol release (Risch et al., 1988; Gold et al., 1988; Kathol et al., 1989; Heuser et al., 1994). In depressed individuals with normal DST suppression, blunted ACTH responses to CRH challenge were not observed.

In response to the poor sensitivity of the DST and CRH stimulation test, Heuser and colleagues (1994) developed a combined DEX-CRH double challenge. Overall, this test is far more sensitive in detecting a major depressive episode (~80%) and has a specificity of 75% for major depressive episodes compared to controls. A number of studies have demonstrated enhanced secretion of cortisol and ACTH to DEX-CRH challenge in depressed individuals compared to controls (Heuser et al., 1994; Holsboer et al., 1995; Zobel et al., 1999; 2001; Baghai et al., 2002). Using the DEX-CRH challenge it has been found that patients who have a high cortisol response following treatment will have a higher risk of relapse within 6 months (Zobel et al., 1999; 2001). Also, it has been repeatedly documented that the resolution of depressive symptoms is correlated with normalization of the HPA axis (Holsboer et al., 1987; Holsboer-Trachsler et al., 1991; Heuser et al., 1994). However, an investigation of healthy individuals at high genetic risk for the development of affective disorders showed abnormal DEX-CRH test results with a cortisol release that was between that of a control group and a group of patients with depression (Holsboer et al., 1995; Modell et al., 1998). Approximately four years later, several of the high-risk healthy individuals were re-tested in the DEX-CRH challenge, and it was found that their cortisol levels were similar to those previously documented (Modell et al., 1998). Thus, abnormal cortisol response to DEX-CRH may represent a vulnerability marker in some individuals (Modell et al., 1998). Ashman and colleagues (2002) suggested that the HPA axis is more reactive in children of depressed mothers. However, it is unknown whether these observations are due to genetic predisposition or increased psychosocial stress resulting from being the offspring of a depressed mother. Rybakowski and Twardowska (1999) have reported that HPA axis dysregulation detected

by the DEX-CRH challenge is far more marked in bipolar depression than in unipolar depression. It has also been suggested that the severity of HPA axis dysregulation increases over the course of the affective illness (Rybakowski and Twardowska, 1999; Zobel et al., 1999), but few studies have documented the number of depressive episodes, duration, and/or type of depressive illness (Christensen and Kessing, 2001).

B. Glucocorticoid Receptors

GRs are the primary focus of attention in the pathophysiology of depression. While dysregulated stress responses are thought to underlie depression in some individuals, one of the primary reasons much of the research has focused on GRs is due to the fact that DEX selectively binds GRs. However, it has been demonstrated that MR activation might also play an important role in the regulation of the HPA axis during the presence of high levels of cortisol by interacting with GRs (Spencer et al., 1998).

Because it is not presently possible to examine MRs and GRs in living human brain tissue, a number of peripheral measurements have been employed to examine GRs specifically. The results of studies examining GR changes in depressed individuals have been mixed, with the majority of studies reporting no change in the binding of GRs in lymphocytes (Schlechte and Sherman, 1985; Maguire et al., 1997) and mononuclear cells (Hunter et al., 1988; Wassef et al., 1992; Rupprecht et al., 1991a; 1991b). However, some studies have reported decreased binding of GRs in mononuclear cells (Gormley et al., 1985; Whalley et al., 1986; Yehuda et al., 1993) and lymphocytes (Sallee et al., 1995) of depressed individuals. Pariante and Miller (2001) have suggested the binding techniques used in these studies may have had an impact on the interpretation of the data.

Postmortem brain has also been used to examine GR mRNA in brain tissue of depressed suicide victims. A study examining GR mRNA in the hippocampus found no difference between depressed suicide victims and healthy controls (Lopez et al., 1998). Another study also found no differences in GR mRNA levels between controls and depressed patients, but did observe decreased GR mRNA in the frontal cortex and hippocampus when data from depressed, bipolar, and schizophrenic individuals were pooled (Webster et al., 2000).

C. The Role of CRH in the Pathophysiology of Depression

It has been suggested that HPA axis dysregulation in depressed individuals is driven by hypersecretion of CRH (Arborelius et al., 1999). Overall, studies examining CRH levels in depressed individuals have been mixed. While a number of studies have observed significantly elevated levels of CSF and plasma CRH in depressed patients (Nemeroff et al., 1984; 1991; Arato et al., 1986; 1989; Banki et al., 1992; Widerlov et al., 1988; Risch et al., 1992; De Bellis et al., 1993; Catalan et al., 1998; Galard et al., 2002), several studies have found no differences (Kling et al., 1991; Molchan et al., 1993; Pitts et al., 1995). Finally, studies using serial CSF sampling observed decreased CRH levels over a 6 hour time frame (Geracioti et al., 1992; 1997).

Post-mortem studies have found differences in CRH levels in the brains of depressed individuals compared to controls. Raadsheer and colleagues (1995) found increased CRH mRNA levels in the PVN of deceased individuals known to have MDD. Another study examining post-mortem brain from male suicide victims found elevations

in CRH levels in the LC, median raphe, and dorsal raphe, while no differences were observed in the medial parabrachial nucleus and dorsal tegmentum (Austin et al., 2003).

Animal models have been extensively used to examine the HPA axis following stressful life events. The maternal separation model of depression has been used to examine behavioral and HPA axis changes in both rodents and non-human primates (Suomi, 1991; Anisman et al., 1998). Animals removed from their mothers either permanently or for unpredictable periods of time, demonstrate behavioral symptoms associated with depression, such as disturbed sleep, altered food intake, and decreased exploratory activity (McKinney et al., 1984). Increases in CRH binding sites in the dorsal raphe nucleus have been observed following maternal separation, in addition to increased CRH immunoreactivity in the parabrachial nucleus (Ladd et al., 1996), which has been implicated in the pathophysiology of depression and anxiety disorders (Weiss et al., 1994). Increased levels of CRH mRNA have also been observed in the central nucleus of the amygdala following maternal separation (Menzaghi et al., 1993). Thus, elevations in CRH activity in both hypothalamic and extrahypothalamic areas may play a role in the pathophysiology of depression. However, the two models described in this report, as well as most models used to reproduce depressive symptoms, place special emphasis on the presence of stressful early life events for the later development of depression. While this may be true for some individuals, it is unlikely that all individuals who develop MDD were subjected to stressful early life events. Thus, questions arise whether the development of depression follows a single common pathway regardless of one's life experience, age, genotypic and/or phenotypic factors, support network, and/or gender, among others. Alternately, it might be that diverse etiological factors can affect specific

neural pathways that are so interconnected that a "final common pathway" concept is more relevant to future research. MDD is recognized as a heterogeneous spectrum disorder; further sub-grouping within the depressed population is imperative in advancing etiological model development.

Finally, CRH antagonists are being examined as potential pharmacological agents in the treatment of MDD (Holsboer, 2003; Zoumakis et al., 2006). A small open-label study explored the use of the CRH_1 receptor antagonist, R121919, as a potential antidepressant in 24 patients with MDD (Zobel et al., 2000). This study found both patient- and clinician-rated depression and anxiety scores improved over the course of treatment. No significant side effects were associated with the administration of R121919 (Kunzel et al., 2003). Larger, double-bind, placebo-controlled trials are required to examine the efficacy of CRH antagonists in the treatment of MDD.

D. Baseline Levels of AVP in Depression

Attempts to examine AVP levels in depressed individuals have been plagued by methodological problems, leading to conflicting results. CSF levels of AVP have been shown to be decreased in depressed patients compared to controls (Gjerris et al., 1985). Numerous studies have reported no change in CSF (Pitts et al., 1995) and plasma AVP levels compared to controls (Raskind et al., 1979; Gjerris et al., 1985; Sörenson et al., 1985; Ritchie et al., 1991). Of these studies, one had a small sample size (Raskind et al., 1979), while two others used neurologically ill patients as controls (Gjerris et al., 1985; Sörenson et al., 1985). One study has shown increased levels of plasma AVP in depressed patients compared to controls (Van Londen et al., 1997). However, the plasma

levels reported in this study are much higher than those reported previously and may be the result of high cross-reactivities reported in the assay procedure (Van Londen et al., 1997). Inder and colleagues (1997) did not find significant differences in AVP levels between a group of depressed subjects (n=45) and healthy controls (n=11) but did find elevated AVP levels in two small subgroups of depressed subjects – those with hypercortisolemia (n=6) and those with suicidal ideation (n=7). Finally, post-mortem studies in depression have shown an increased number of AVP-expressing neurons in the PVN of the human hypothalamus in depression (Purba et al., 1996), while another study found increased numbers of AVP-immunoreactive neurons in the suprachiasmatic nuclei of depressed individuals compared to controls (Zhou et al., 2001).

In addition to cross-reactivity issues in specific assays, there are other measurement issues that add to the difficulty in interpreting data across sources. Single time-point measurements have been used in all studies examining AVP levels. Since plasma AVP levels are subject to random fluctuations (Rubin et al., 1978; Lavie et al., 1980; Brandenberger et al., 1998), multiple sampling over a period of time and area under the curve measurements are better indicators of AVP levels in plasma. As previously reviewed, the source of plasma AVP is an ongoing concern.

While AVP and CRH are both ACTH secretegogues and are thought to act in a synchronous manner in stimulating the release of ACTH, there are presently no data available on the interaction of the two neuropeptides in depressed individuals. Meaney and colleagues (1996) have suggested that early life stress affects patterns of CRH and AVP gene expression, synthesis, and/or release and thus may play a role in the sensitivity of the HPA axis and the subsequent development of MDD, PTSD, and other disorders

associated with early stressful life events. A study by Nakase and colleagues (1998) has also documented increases in AVP and CRH mRNA levels in the PVN of adult rats who were exposed to walking stress. Thus, both early and later life stress have the ability to induce changes in the regulation of CRH and AVP synthesis and release and may play a role in the development and pathophysiology of depression.

One novel attempt at sub-grouping the depressed population has recently emerged. Recent research results emerging from a group in the Netherlands have suggested that an anxious-retarded subtype of depression can be derived from the DSM-IV category of melancholia (de Winter et al., 2003). The anxious-retarded subtype is characterized by three primary dimensions of emotional dysregulation, autonomic dysregulation, and motivational inhibition (de Winter et al., 2004). Autonomic dysregulation is associated with somatic anxiety, while motivational inhibition is associated with psychomotor retardation and anhedonia. Additionally, anxious-retarded depression has been associated with a family history of depression (de Winter et al., 2004), but more importantly for this discussion, elevated plasma levels of AVP and cortisol (de Winter et al., 2003; Goekoop et al., 2006). This association was not established for the purely melancholic form of depression. Earlier evidence noted an association between psychomotor retardation in depression and higher levels of AVP (Van Londen et al., 1998). Since the subtype of anxious-retarded depression is not currently included in the DSM-IV and most of this research has been carried out by the same research group, further studies are required by independent and external groups to corroborate data not only for the classification of anxious-retarded depression, but also the elevated AVP levels observed in this phenotype of depression.

E. Challenge Studies of AVP in Depression

Several groups have attempted to challenge the vasopressinergic system in individuals with MDD using AVP and its analogues. Cortisol and/or ACTH output were used as a means of assessing HPA axis function. Overall, these studies have had inconsistent findings, but this may be a reflection of the sample populations examined, the severity of depression in subjects examined and/or the type and dose of AVP administered during the challenge. Meller and colleagues (1987) observed normal ACTH and increased cortisol responses to AVP infusion in 27 subjects with either MDD or bipolar disorder during an active major depressive episode compared to a control group. Another study by Kathol and colleagues (1989) noted non-significant trends toward a decrease in ACTH and an increase in cortisol levels (Kathol et al., 1989).

Two studies have also been carried out using the AVP analogue, desmopressin (DDAVP), to challenge the HPA axis (Malerbi et al., 1996; Dinan et al., 1999). Malerbi and colleagues (1996) found no differences in ACTH and cortisol between individuals with MDD and controls following DDAVP infusion. In the second study, individuals with MDD underwent CRH infusion on the first visit and CRH+DDAVP infusion on the second visit (Dinan et al., 1999). The responses between the two visits were then compared. Following CRH infusion alone, ACTH output was blunted compared to controls. However, following CRH+DDAVP infusion, the ACTH response was indistinguishable between depressives and healthy controls. This is consistent with animal studies that have noted a downregulation of CRH_1 receptors and an upregulation of V_{1b} receptors in models of chronic stress (Scott and Dinan, 2002).

F. Conclusions Regarding Dysregulation of the HPA Axis in MDD

Current evidence supports dysregulation in the HPA axis for some individuals with MDD. Basal hypercortisolemia and alterations in patterns of cortisol release occurring after pharmacological challenge with DEX or DEX/CRH administration have not been universally observed. In fact, even though it is the most commonly used pharmacological challenge used in MDD, cortisol non-suppression following DEX administration has only been observed in approximately 50% of depressed individuals (Christensen and Kessing, 2001). These observations raise questions regarding the biological heterogeneity of MDD and the involvement of the HPA axis dysregulation in the generation of depressive symptoms. Currently, there is little convincing evidence that elevated cortisol levels actually contribute to depressive symptoms.

The role of CRH in the pathophysiology of MDD is a promising area of research. In particular, further research regarding the neuromodulatory roles of extrahypothalamic CRH in areas of the brain known to be involved in the regulation of mood and anxiety is necessary. Regarding the HPA axis, the interaction between AVP and CRH in MDD needs to be examined further. While CRH hypersecretion in individuals with MDD is likely, it is unknown whether this occurs as a result of hypothalamic or extrahypothalamic dysfunction. Current evidence does not support changes in AVP levels in MDD. Future research should measure AVP and CRH simultaneously in MDD as imbalances in the release of one or both neuropeptides may contribute to HPA axis dysregulation.

V. HPA AXIS AND PTSD

As in MDD, changes in HPA axis functioning have been observed in PTSD. Animal models of stress provided initial evidence that fear and anxiety were connected to changes in the functioning of the HPA axis. While an adequate animal model of PTSD has not been established, early work involving animal models led researchers to examine the link between serious trauma and potential changes in the functioning of the HPA axis.

Much of the research involving PTSD and the HPA axis has involved the measurement of baseline levels of cortisol and changes in cortisol levels resulting from DEX challenge. The literature involving other neuropeptides involved in the HPA axis cascade such as AVP, CRH, and β-END is not quite as extensive, but preliminary work has been carried out with both CRH and β-END.

A. Cortisol Findings in PTSD

Baseline studies examining 24 hour urinary and single point cortisol measurements in individuals with PTSD have been conflicting. Lower levels of cortisol have been reported in PTSD patients in some (Mason et al., 1986; Yehuda et al., 1995; Goenjian et al., 1996; Boscarino, 1996; Delahanty et al., 2000; Kanter et al., 2001; Rohleder et al., 2004), but not all, studies (Pitman and Orr, 1990; Lemieux and Coe, 1995; Maes et al., 1998; Thaller et al., 1999).

The DST has been extensively used to challenge the HPA axis in PTSD patients. Due to initial observations that 1mg of DEX caused enhanced cortisol suppression in individuals with PTSD (Halbreich et al., 1989; Kosten et al., 1990), the low dose DST (0.5mg) was introduced (Yehuda et al., 1993). In recent years, some researchers have

even used a 0.25mg dose of DEX to challenge the HPA axis in subjects with PTSD. Unlike the 1mg dose of DEX, no standard cut-off value for cortisol suppression has been determined in the literature for DEX doses lower than 1mg.

A recent review by de Kloet and colleagues (2006) summarized all studies using the DST in individuals with PTSD. Overall, most studies demonstrated enhanced cortisol suppression in PTSD patients compared to controls using 0.25mg (Yehuda et al., 1995), 0.5mg (Yehuda et al., 1993; 1995; 2002; 2004; Stein et al., 1997; Newport et al., 2004), and 1mg (Halbreich et al., 1989; Atmaca et al., 2002) doses of DEX. In contrast, a small number of studies did not demonstrate enhanced cortisol suppression following DEX administration (Kudler et al., 1987; Kosten et al., 1990; Thaller et al., 1999; Lindley et al., 2004). Enhanced cortisol suppression in PTSD patients appears to be unaffected by different types of trauma, medication status, or comorbid psychiatric conditions. However, it has been suggested that the frequency of cortisol non-suppression is higher in PTSD patients with comorbid MDD (de Kloet et al., 2006). Therefore, the inclusion of subjects with comorbid PTSD and MDD may produce a different neuroendocrine pattern of response compared to those with one of the disorders alone.

Increased cortisol suppression in PTSD patients has often been attributed to enhanced negative feedback on the HPA by cortisol. In response to psychosocial challenge, PTSD subjects demonstrated elevated cortisol release in both the anticipation phase and during the challenge (Bremner et al., 2003; Elzinga et al., 2003). Additionally, increased GR density has been observed in mononuclear leukocytes, potentially demonstrating enhanced feedback sensitivity of the HPA axis (Yehuda et al., 1991; 1993;

1995; Stein et al., 1997). However, this has not been demonstrated in all studies (Yehuda et al., 2002; 2004; Gotovac et al., 2003; Rohleder et al., 2004).

As reviewed by de Kloet et al. (2006), the HPA axis has also been challenged using CRH and ACTH. Overall, studies using CRH and ACTH challenge have been inconsistent, with conflicting results (Smith et al., 1989; Rasmusson et al., 2001; Kellner et al., 2003).

B. CRH Hypersecretion in PTSD

As observed in MDD, basal CRH concentrations are increased in the CSF of PTSD patients (Bremner et al., 1997; Baker et al., 1999). Many authors attempt to link elevations in CRH in subjects with PTSD to the HPA axis since changes in basal cortisol levels and glucocorticoid feedback have been observed (Baker et al., 1999; Kasckow et al., 2001, Strohle and Holsboer, 2003; Claes, 2004). While it is unknown why elevations in CRH are associated with very different symptom clusters such as those observed in MDD and PTSD, it is likely that CRH dyregulation in different neural pathways contribute to the observed psychopathology in these two disorders.

In addition to its role in the HPA axis cascade, CRH plays important roles in other brain regions associated with the generation, maintenance, and termination of fear and anxiety responses. These include regions such as the amygdala, LC, BNST, PFC and hippocampus. Each of these brain regions have also been implicated in the pathophysiology of PTSD, as supported by preclinical data and neuroimaging studies looking at neuroanatomical differences between subjects with PTSD and healthy

controls. Therefore, while it is tempting to associate CRH hypersecretion with HPA axis dysregulation, CRH dysregulation in other areas of the CNS can more appropriately explain some of the symptoms observed in PTSD. CRH represents one of the few known peripheral markers of dysfunction within the limbic system, but due to its primary role within the HPA axis cascade, it is often considered a marker of HPA axis dysregulation.

Amygdalar CRH projections to multiple areas of the limbic system play a stimulatory role during anxiety and fear-provoking events. As discussed by Kim and Gorman (2005), the amygdala initiates and coordinates fear responses by interacting with other brain regions involved with the production of physiological stress responses. Furthermore, the amygdala plays a key role in the production and storage of fearful memories associated with emotionally significant traumatic events. Lesioning of the amygdala has been shown to attenuate fear responses to angry voices, loud noises, and other stimuli that would normally provoke emotional and anxious responses (Rolls, 1984; Kim and Gorman, 2005). The role of the amygdala in the production of traumatic memories is particularly significant, since one of the key features of PTSD involves re-experiencing of memories associated with the trauma(s). Indeed, heightened activation of the amygdala has been noted in subjects with PTSD compared to healthy controls during the presentation of traumatic imagery and emotionally significant stimuli (Anand and Shekhar, 2003; Shin et al., 2004; Stein et al., 2007; Bryant et al., 2007). Increased cerebral blood flow has also been documented in the amygdala in PTSD patients (Liberzon and Phan, 2003). It is presently unknown how CRH neurotransmission in the amygdala is affected by changes in amygdalar functioning in individuals with PTSD, since the measurement of in vivo CRH levels and assessment of CRH receptor

functioning in specific regions of human brain is not currently possible. Since CRH plays a stimulatory role in the amygdala, it is possible that increased amygdalar activity in subjects with PTSD could lead to further release of CRH, thus contributing to the increased CSF CRH levels observed in PTSD.

Stress models in animals have been instrumental in elucidating some of the physiological effects of CRH and its possible role in anxiety disorders. CRH is elevated in several brain regions, primarily the amygdala, hippocampus, PFC, and LC (Wiersma et al., 1993; 1998; Asbach et al., 2001; O'Donnell et al., 2004; Merali et al., 2004; Broadbear, 2006), during fear and arousal in animals. Neuroanatomical changes have also been noted in the amygdala, hippocampus and PFC in subjects with PTSD (Kim and Gorman, 2005; Karl et al., 2006). CRH has been found to increase LC neuronal firing, and this effect can be attenuated by CRH_1 receptor antagonists (Asbach et al., 2001; Jedema and Grace, 2004). Noradrenergic dysregulation has been implicated in PTSD, and, while beyond the scope of this thesis, may be responsible for many of the autonomic, hyperarousal symptoms observed in subjects with PTSD (O'Donnell et al., 2004). The LC is also closely associated with CRH projections from the amygdala. Thus, increases in extrahypothalamic CRH may produce profound behavioral changes associated with PTSD in its role as a neurotransmitter and neuromodulator within the limbic system.

C. AVP

As discussed earlier, AVP and CRH are co-secretagogues of ACTH and are responsible for the initiation of the HPA axis cascade. Animal research has implicated

AVP in the generation of fear and anxiety responses, and patterns of release may vary as a function of the stressor involved (Scott and Dinan, 1998). This has important implications for individuals with PTSD, where traumatic events causing PTSD symptoms can have physiological and/or psychological components. Despite its ability to act as an ACTH secretagogue, the role of AVP in PTSD has been relatively ignored. No studies have examined AVP levels in individuals with PTSD. Furthermore, clinical trials with V_{1b} receptor antagonists, demonstrating anxiolytic properties in rodents, have not yet been carried out in PTSD patients. Thus, the roles of AVP in the emergence and maintenance of specific PTSD symptoms are still inconclusive and further research is warranted.

VI. HPA AXIS CHANGES IN INTERPERSONAL TRAUMA

A. Animal Models of Early Life Stress

It is recognized that genetic susceptibility and environmental stress may contribute to the development of stress-related psychiatric sequelae. Individuals exposed to early adverse life events are predisposed to the development of anxiety and affective disorders later in adulthood (Heim and Nemeroff, 1999). Childhoods that are characterized by neglect, abuse, instability, and adversity are frequently associated with poor health outcomes. While poverty and low socioeconomic status (SES) have been associated with increased risk of psychopathology, variations in parental care appear to be more important in the mediation of intellectual and emotional development. In fact, when the quality of parental care is controlled, SES has no significant impact on childhood development (Conger et al., 1994; Fish et al., 2004). Low SES may negatively

affect the emotional state of the parents, leading to higher levels of depression, irritability, anxiety, and stress, impacting parent-child interactions and potentially leading to more punitive forms of punishment (Conger et al., 1994; Belsky, 1997).

The importance of attachment between mother and child has been highlighted by both social and biological scientists as an important variable in the development of a well-adjusted individual (Vaughn et al., 1979; Morton and Browne, 1998; Moriceau, 2005). A number of animal models have employed variations in maternal care as a means with which to study postnatal stress. While numerous variables involved in the development of a child may contribute to early life stress or aversive stimuli, the bond between mother and child is particularly important and easier to examine using animal models of early life stress.

Animal models using postnatal handling, maternal separation, and repetitive pain or restraint have demonstrated that neuroendocrine responses can be influenced by early life stress well into adulthood (Anand et al., 1999; Hennessy et al., 1999; Liu et al., 2000; Cirulli et al., 2003; Maccari et al., 2003). Long-term changes in brain plasticity as a result of early environmental adversity likely contribute to individual differences in physiological and behavioral responses to stress (Cirulli et al., 2003). Glucocorticoids appear to be particularly influential in determining the course of prenatal (Seckl, 1998) and postnatal (Fish et al., 2004) brain programming. In the subsequent paragraphs, key findings will be highlighted. For more in-depth reviews, interested readers are referred elsewhere (Meaney et al., 1996; Cirulli et al., 2003; Maccari et al., 2003; Fish et al., 2004).

A recent review by Fish and colleagues (2004) highlighted a body of literature examining the long-term effects of maternal care on offspring in rodents. Researchers sought to examine the impact of naturally occurring variations in maternal care on stress response pathways and used licking/grooming (LG) behaviors and arched back nursing (ABN; positive behavior associated with increased access to feeding) as determinants of high or low maternal care. Regardless of whether the rodent received high or low amounts of LG-ABN, all fell within the normal range of maternal care for the species and no mother was classified as disinterested or neglectful.

Collectively this series of studies demonstrates that variations in maternal behavior that still fall within the normal range of care for a given species may have vast implications for the development of behavioral and physiological correlates of stress response. Overall, offspring that received low levels of LG-ABN appear more reactive to stressful stimuli both behaviorally and physiologically. Fish and colleagues (2004) clarify that the transmission of individual differences in stress reactivity is not genomic in nature by citing studies that have employed reciprocal cross-fostering of offspring of high and low LG-ABN mothers (O'Donnell et al., 1994; Francis and Meaney, 1999; Francis et al., 1999; Francis et al., 1999; Caldji et al., 2003). These studies demonstrated that the quality of maternal care was a strong determinant in stress reactivity and that offspring of low LG-ABN mothers raised by high LG-ABN mothers had phenotypic traits similar to offspring of high LG-ABN mothers.

A number of studies have examined maternal separation and postnatal handling as a means with which to examine the long-term consequences of neonatal rearing in rats. Overall, postnatal handling appears to attenuate the reactivity of stress response pathways

through important behavioral and neuroendocrine mechanisms. Meaney and colleagues (1988, 1989) have demonstrated increased glucocorticoid release and decreased feedback sensitivity to elevated glucocorticoids levels in non-handled versus handled rats. Additionally, handling increased GR binding capacity in the hippocampus of adult animals. Chronic administration of corticosterone to adult rats handled as neonates significantly reduced the binding capacity of the GR such that there were no differences between handled and non-handled adult rats. These data suggest that increases in glucocorticoids as a result of heightened stress reactivity in non-handled rats may mediate differences in hippocampal damage between handled and non-handled rats later in life.

Differences in CRH synthesis and release have also been observed in postnatal handling models. A 2.5-fold increase in CRH mRNA and peptide levels in the hypothalamus has been observed in non-handled compared to handled animals (Plotsky and Meaney, 1993). CRH release from the hypothalamus was also heightened in non-handled animals. A more recent study by Plotsky and colleagues (2005) found increased CRH-like immunoreactivity and mRNA levels in the PVN, central nucleus of the amygdala, BNST, and LC in non-handled rats and handled rats with daily maternal separations of 180 minutes versus controls (animals reared in a handling facility with brief twice handling during weekly cage changes). The handled rats with 180 minute maternal separation also demonstrated normal circadian troughs of ACTH and cortisol but hypersecretion in response to airpuff startle and a 40% decrease in CRH_1 receptors versus controls. Finally, transient increases in the central nucleus of the amygdala CRH mRNA at day 6, as well as a prolonged decrease in PVN CRH at day 9 have been observed in handled rats (Fenoglio et al., 2004).

The impact of maternal separation on neuroendocrine measures has also been examined extensively. Six hour separation in the first two weeks of life results in decreased glucocorticoid binding in the hypothalamus and hippocampus, while 180-360 minute separations for the first two weeks of life result in increased plasma ACTH and cortisol response to stress (Plotsky et al., 1993).

Taken together, rodent models of maternal care and early life stress suggest that environmental interactions in the early postnatal period are important determinants of long-term stress response. The quality of postnatal care appears to be particularly important in the structuring of stress response pathways, where early life stress appears to influence behavioral, cognitive and physiological responses to adverse stimuli later in life. Early adverse conditions appear to result in amplification of stress responsivity later in life. While it would make sense that early biological and behavioral adaptations to early life stress may prepare individuals for later stressors as adolescents and adults, the survival value of the observed changes are questionable. Rodent models examining the impact of low levels of postnatal care, maternal separation, and handling on adult offspring all noted hypersecretion of glucocorticoids as a result of acute stressors and reduced negative feedback via GC receptors. Prolonged elevations of glucocorticoids are neurotoxic in various brain regions, including the hippocampus and, thus, it is possible that while hippocampal volumes were not measured in the animal models, hippocampal damage was present. Hippocampal damage has been observed in both depression and PTSD and has been postulated to result from glucocorticoid neurotoxicity (Sapolsky, 2000; 2001).

In addition to observations related to glucocorticoids, pathways involving CRH have also been found to be modified as a result of early life stress models in rodents. The impact of heightened CRH release in rats experiencing early life stress is quite profound as it plays key roles in the regulation of both physiological and psychological stressors through its involvement in both the HPA axis and central nucleus of the amygdala. Elevated levels of CSF CRH have been observed in both depression and PTSD and are thought to underlie many of the symptoms observed in both disorders.

There has been some criticism that rodent models of early life stress are not reflective of early adverse stimuli experienced by humans. However, as stated by Cirulli and colleagues (2003), "basic neurobiological research has firmly established that the mother acts as a regulator of the infant's states". Indeed, studies have documented the importance of mother-child interactions on growth and development across species (Kuhn et al., 1990).

B. HPA Axis Changes in Individuals Exposed to Interpersonal Trauma

B.1. Baseline Cortisol Changes in IT

While there is a large body of evidence associated with HPA axis changes in individuals with MDD or PTSD, literature examining HPA axis changes specific to female survivors of IT is still in its infancy. Research to date has focused almost exclusively on baseline levels of cortisol and changes in cortisol release following psychosocial or pharmacological challenge. However, there are a number of sample selection issues that complicate interpretation of these studies as a whole. Survivors of IT often present with complex clinical pictures and tend to be a clinically heterogeneous

group. While many survivors of IT have no psychiatric sequelae associated with their past trauma, some may have subtheshold or full diagnoses of MDD and/or PTSD as well as features of other psychiatric disorders such as anxiety, substance abuse, and DIDs. Further, survivors of IT may have experienced single incidents of physical and/or sexual trauma in either childhood or adulthood or may have experienced multiple incidents over the course of their lifetime. Others may have experienced more chronic IT in the form of prolonged childhood abuse or IPV.

These factors present significant challenges to examining HPA axis changes associated with IT. A prominent issue in these studies appears to be the methodology surrounding the selection of samples of IT survivors. Many researchers have chosen to recruit subjects on the basis of IT experiences such as CPV, CSA, adult rape, or IPV. Doing so led to homogeneous populations of IT survivors on the basis of experience, abuse severity and period of life during which trauma occurred. However, most of these studies did not control for psychiatric diagnoses within samples of IT survivors. Previous research has demonstrated that psychiatric disorders (such as MDD and PTSD) can influence changes in the HPA axis. Since many survivors of IT have partial or full diagnoses of MDD and/or PTSD, ignoring psychiatric status may confound data examining cortisol levels in this population.

While it would be ideal to create homogeneous groups of IT survivors on the basis of psychiatric classification, many individuals in this population have complex psychiatric histories and symptoms that do not easily fit into DSM-IV diagnostic criteria. HPA axis literature has historically examined individuals with full DSM-IV diagnoses. What does one do then with individuals that only meet partial criteria for DSM-IV

diagnoses and/or may have had met full diagnostic criteria in the past and may again in the future? While they do not easily fit into DSM-IV diagnoses, the severity of impairment in their daily lives with regard to social, occupational, and family functioning can be pervasive and devastating. However, with regard to HPA axis research, it has been shown that that the use of use of full diagnostic criteria, as opposed to scale cut-offs or sub-threshold cases (Aardal-Eriksson et al 2001; Hawk et al 2000), lifetime versus current diagnosis (Boscarino 1996; Yehuda et al 2002), and psychiatric comorbidity (Rasmusson et al 2001) may impact cortisol levels.

Other individual variables such as age, sex, reproductive status, hormonal treatment (Ferrari et al., 2001; Kirschbaum et al., 1999; Seeman et al., 2001), birth weight (Reynolds et al., 2001), psychotropic treatment (Holsboer and Barden 1996; Kraus et al., 1988; Meador-Woodruff and Greden, 1988), substance use or dependence (Costa et al., 1996; Sarkola et al., 2001), and cigarette smoking (Pickworth and Fant, 1998) can also affect measured cortisol levels. Since cortisol levels are affected by so many variables and IT survivors are, by nature, a clinically heterogeneous group, comparing studies that have looked at cortisol without regard for the many confounding variables provides little clarity. Each study represents an interpretation of which independent variables the researchers felt would impact cortisol levels, the dependent variable. The logistics of recruitment of this highly vulnerable population often necessitate broad inclusion criteria to ensure sufficient numbers of study participants, especially if the research design requires an unmedicated sample. Thus, most studies represent a microcosm of the population as a whole and while these data are still important, it is not feasible to compare cortisol changes in fundamentally different samples of IT survivors. Studies that

carefully restrict confounding variables involving large multi-site recruitment or pooling of subject data across research groups may serve as potential strategies to address the diversity of outcomes of this study population.

As mentioned earlier, most studies examining the HPA axis in IT survivors have looked exclusively at cortisol levels. Table 3 highlights studies examining baseline cortisol levels in survivors of sexual assault (Resnick et al., 1995; Yehuda et al., 1998), childhood sexual and physical abuse (De Bellis et al., 1999; Carrion et al., 2002; Altemus et al., 2003), and IPV (Seedat et al., 2003; Pico-Alfonso et al., 2004; Inslicht et al., 2006). Although most studies did not control for all potential confounds (e.g. Axis I diagnoses, medication status, current adversity, the method of cortisol sampling, and the timing of sample collection), there are some early trends that are worth highlighting.

Table 3: Baseline Cortisol Levels in IT

REFERENCE	POPULATION/ TYPE OF IT	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
Resnick et al. (1995)	Sexual assault (n=57) Rape victims were identified in an emergency room and were evaluated for assault severity as well as prior history of physical or sexual assault within 51 hours of the assault.	PTSD No other psychiatric disorders were cited. Medication status unknown.	None	Plasma cortisol levels taken at the time of presentation to the emergency room.	Women with a history of physical or sexual assault had significantly attenuated cortisol levels in response to the sexual assault compared to women without previous histories of IT. Only women who had never been assaulted had higher cortisol levels. Women with previous assault histories had a higher probability of developing PTSD.
Yehuda et al (1998)	Sexual assault (n=20) Rape victims were identified in an emergency room and were evaluated for assault severity as well as prior history of physical or sexual assault.	PTSD No other psychiatric disorders were cited. Medication status unknown.	None	Plasma cortisol levels taken at the time of presentation to the emergency room.	Women with a history of physical or sexual assault had significantly attenuated cortisol levels in response to the sexual assault compared to women without previous histories of IT. PTSD status at 3 month follow-up was not related to cortisol levels but was related to a prior history of assault and higher injury rape.

REFERENCE	POPULATION/ TYPE OF INTERPERSONAL TRAUMA	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
De Bellis et al (1999)	Abused children with PTSD (n=18), Non-traumatized children with overanxious disorder (n=10), healthy controls (n=24) Abuse is defined as physical or sexual abuse and neglect. Males were included and children were aged 8-13.	PTSD MDD Exclusion criteria included meeting DSM-III criteria for anorexia nervosa, bulimia nervosa, autism, or schizophrenia. All subjects were medication free	None	24 hour collection of urinary free cortisol	Maltreated children with PTSD had greater excretion of urinary free cortisol than controls.
Carrion et al (2002)	Traumatized children with PTSD (n=51) and controls (n=31) Multiple types of trauma were included such as witnessing violence, physical and sexual abuse, among other. Males were included and children were aged 7-14.	PTSD MDD Attention Deficit Hyperactivity Disorder Separation Anxiety Specific Phobia Social Phobia Exclusion criteria includes history of substance abuse disorder. Medication status unknown.	None	Salivary cortisol levels were collected 4 times per day (pre-breakfast, pre-lunch, pre-dinner, pre-bed) for 3 consecutive days.	Clinical group had elevated cortisol compared to controls. Girls with PTSD symptoms had higher cortisol than boys with PTSD symptoms.
Altemus et al (2003)	Childhood IT related PTSD (n=16) and healthy controls (n=15) History of childhood sexual or physical abuse	PTSD MDD Anxiety Disorders Some patients were medicated.	None	Single point salivary cortisol levels	No differences in cortisol levels between controls and PTSD patients

REFERENCE	POPULATION/ TYPE OF IT	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
Seedat et al (2003)	IPV (n=22), healthy controls (n=16) Physical or sexual abuse in an intimate partner relationship.	PTSD MDD Anxiety disorders Exclusion criteria included psychotic disorders, substance abuse, and bipolar disorder. All subjects were medication free.	None	Morning plasma cortisol levels (between 9am and 12pm).	Mean cortisol levels were lower in IPV subjects than in controls
Pico-Alfonso et al (2004)	Physical (n=70) or psychological (n=46) IPV, healthy controls Physical IPV includes both physical and sexual abuse. Psychological abuse includes verbal attacks and threats, control and power, harassment, stalking, and blackmail, among others.	PTSD MDD Anxiety disorders Some subjects were medicated.	None	Salivary cortisol at 8am and 8pm on 4 consecutive days.	IPV subjects had higher cortisol levels in the evening compared to controls.
Inslicht et al (2006)	IPV with (n=29) and without (n=20) PTSD Physical or sexual abuse in an intimate partner relationship.	PTSD MDD Other psychiatric disorders were not noted. Some patients were medicated.	None	Salivary cortisol at 1, 4, 9, and 11 hours after awakening	IPV group with PTSD had higher cortisol levels than group without PTSD over course of the day.

Rape survivors who had been previously assaulted had lower levels of plasma cortisol immediately following the assault and were at higher risk of having PTSD 3 months later (Resnick et al., 1995; Yehuda, 1998). Future prospective studies that examine the link between severe trauma in adult females may help elucidate the link between the development of mood and anxiety disorders and HPA axis dysregulation at the time of and in the period immediately following the trauma. The diagnostic criteria for PTSD include a duration criterion of 1 month, which adds the difficulty of relating emerging HPA axis changes to PTSD. MDD has a similar, albeit shorter duration criterion of 2 weeks.

Studies looking at basal plasma cortisol levels in survivors of IPV have been inconsistent. While one group found decreased levels of plasma cortisol in the morning in survivors of IPV compared to controls (Seedat et al., 2003), another group found no differences in the morning, but found increased levels of plasma cortisol in the evening (Pico-Alfonso et al., 2004). Another group found plasma cortisol levels to be elevated over the course of the entire day in IPV survivors with PTSD compared those without PTSD diagnoses (Inslicht et al., 2006). All three studies included participants with a number of different mood and anxiety disorders and two included subjects who were medicated with psychotropic drugs at the time of sampling (Pico-Alfonso et al., 2004; Inslicht et al., 2006). Women who have experienced IPV and those who have experienced childhood IT are not independent samples, making it difficult to relate adult changes to specific experiences in the subgroup that has experienced both. However, single point salivary cortisol measurements in adult survivors of childhood sexual and physical abuse with PTSD showed no differences between controls and the clinical group (Altemus et

al., 2003). In contrast, Lindley and colleagues (2004) observed elevated salivary cortisol levels at baseline in a group of adult CIT survivors with only PTSD (all other Axis I psychiatric disorders were excluded).

Two pediatric studies examined basal cortisol levels in child survivors of IT with PTSD diagnoses in 24 hour urinary free cortisol collections (De Bellis et al., 1999) and saliva samples taken at 4 different times points over the course of a day (Carrion et al., 2002). Both studies found elevated cortisol levels in the clinical groups compared to control groups of children. Carrion and colleagues also found that female children with abuse histories and PTSD symptoms had higher cortisol levels than male children with similar abuse histories and PTSD symptoms. As discussed previously, early life stressors can have long lasting impact of HPA axis activity. Thus, these changes observed in children may persist into adulthood and account for changes seen in adult survivors of childhood IT, irrespective of other adult experiences.

B.2. Psychosocial Challenge Studies of the HPA Axis in IT Survivors

Unlike studies looking at baseline levels of cortisol in survivors of IT, findings from studies examining psychosocial or pharmacological challenge of the HPA axis in survivors of IT are more consistent. Table 4 summarizes studies that have employed psychosocial challenges with a focus primarily on survivors of CPA and CSA. Psychosocial challenge studies suggest that cortisol hypersecretion occurs in survivors of CIT with PTSD or MDD during psychosocial stressors. Additionally, the study by Heim and colleagues suggests ACTH hypersecretion may also occur in survivors of CIT with MDD. Future research needs to replicate these findings as well explore other elements of

HPA axis signalling such as CRH, AVP, ACTH, and GRs to elucidate the potential mechanisms of cortisol hypersecretion of CIT survivors with MDD or PTSD in response to psychosocial stressors.

TABLE 4: Cortisol Levels Following Psychosocial Challenge in IT Survivors

REFERENCE	POPULATION/ TYPE OF INTERPERSONAL TRAUMA	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
Heim et al (2000)	CIT+MDD (n=14), CIT-MDD (n=14), MDD-CIT (n=10), healthy controls (n=12) CIT includes childhood sexual or physical abuse	PTSD MDD Anxiety disorders Exclusion criteria included psychotic disorders, substance abuse, and bipolar disorder. All subjects were medication free.	Public speaking and arithmetic tasks.	Plasma ACTH and cortisol levels were measured at baseline and in response to psychosocial stressor.	CIT+MDD had higher peak cortisol and ACTH compared to controls and MDD-CIT. CIT+MDD had higher peak cortisol compared to CIT-MDD. CIT-MDD had higher peak ACTH levels versus controls. All groups had similar baseline ACTH and cortisol levels.
Elzinga et al (2003)	Abuse related PTSD (n=12), trauma controls (n=12) History of sexual or physical abuse	PTSD MDD Anxiety Disorders Some patients were medicated	Personalized traumatic script.	Salivary cortisol at several time points before and after challenge.	PTSD patients displayed elevated cortisol levels in anticipation phase, during and after challenge.
Bremner et al (2003) Note: This study included males and females	Abuse-related PTSD (n=23), healthy controls (n=18) History of childhood sexual or physical abuse.	PTSD MDD Anxiety Disorders Schizophrenia, substance abuse and eating disorders were excluded.	Arithmetic cognitive tasks with negative feedback	Salivary cortisol at several time points before and after challenge.	Cortisol elevated in anticipation phase and in response to challenge in both groups, PTSD group displayed elevated cortisol levels in anticipation phase and during challenge.

B.3. Pharmacological Challenge Studies of the HPA Axis in IT Survivors

In addition to psychosocial challenge, neuroendocrine challenge paradigms have been used to examine the HPA axis in survivors of IT. Most studies employing pharmacological challenge were carried out in survivors of CIT. These studies are summarized in Table 5. Because many of the pharmacological challenge studies were carried out in fundamentally different samples of CIT survivors, it is difficult to compare outcomes between studies. Future work must replicate these findings as well as explore the relationship between different forms of IT such as adult trauma, IPV, and CIT and HPA axis dysregulation occurring as a function of psychiatric morbidity in pharmacological challenge studies. Additionally, like baseline and psychosocial challenge studies of the HPA axis in IT survivors, researchers must be diligent about recruiting homogenous IT samples.

TABLE 5: Pharmacological Challenge Studies in IT Survivors

REFERENCE	POPULATION/ TYPE OF IT	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
Stein et al (1997)	Severe CSA (n=19) and healthy controls (n=21) History of severe CSA	PTSD MDD Dissociative Disorders Some patients were medicated	DEX (0.5mg)	Plasma cortisol suppression and density of lymphocyte glucocorticoid receptors	Women with history of CSA had enhanced cortisol suppression compared to healthy controls. No significant differences in mean lymphocyte GR density.
Lindley et al (2004)	CIT with PTSD/medicated (n=17), CIT with PTSD/unmedicated (n=17), healthy controls (n=17) CIT groups had a history of childhood sexual or physical abuse.	PTSD All other Axis I disorders were excluded.	DEX (0.5mg)	Salivary cortisol was measured at 8am, 4pm, and 10pm on days before and after DEX was taken	Higher baseline levels of cortisol were observed in the PTSD group. There were no significant differences in responses to DEX.
Newport et al (2004)	CIT (n=19), CIT+MDD (n=16), MDD-CIT (n=10), healthy controls (n=19) CIT has a history of childhood sexual or physical abuse.	PTSD MDD Anxiety disorders Exclusion criteria included psychotic disorders, substance abuse, eating disorders and bipolar disorder. All subjects were medication free.	DEX (0.5mg and 1mg)	Pre-DEX plasma samples were collected at 8am and 1pm. Post-DEX samples were collected at 8am and 4pm. Plasma samples were collected for cortisol and ACTH measurements.	No significant group differences were noted at the 1mg dose. At the 0.5mg dose, the CIT+MDD group had greater cortisol and ACTH suppression to DEX when compared to all other groups.

REFERENCE	POPULATION/ TYPE OF IT	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
Rasmussen et al (2001)	PTSD (n=12) and healthy controls (n=11) 11/12 of the PTSD group had experienced IT in the form of physical or sexual abuse in either childhood or adulthood.	PTSD MDD Anxiety Disorders Substance Abuse All were medication free	CRH (1μg/kg) and ACTH (250μg) stimulation tests	CRH Challenge: Plasma ACTH and cortisol measurements were taken every 15 min from -15min to +120 after the IV infusion of CRH. ACTH Challenge: Plasma cortisol samples were taken at baseline, +30min and +60min after infusion of IV ACTH.	Baseline cortisol and ACTH levels did not differ between the two groups. The PTSD group had greater cortisol and ACTH responses to CRH infusion. The PTSD group also showed a greater cortisol response to ACTH infusion.
Heim et al (2001)	CIT with MDD (n=15), CIT without MDD (n=20), MDD with no CIT (n=11), healthy controls (n=20) History of childhood physical or sexual abuse.	PTSD MDD Anxiety Disorders Exclusion criteria included psychotic disorders, substance abuse, and bipolar disorder. All subjects were medication free.	CRH (1μg/kg) and ACTH (250μg) stimulation tests	CRH Challenge: Plasma ACTH and cortisol measurements were taken at -150, -120, -90, -60, -30, +5, +15, +30, +60, +90, and +120 minutes. ACTH Challenge: Plasma cortisol samples were taken at -30, 0, +30, +60, +90, +120, +150, and +180 after infusion of IV ACTH.	CIT-MDD had elevated ACTH responses to CRH. CIT+MDD and MDD-CIT groups had blunted ACTH responses to CRH. CIT-MDD had lower baseline and stimulated cortisol levels after ACTH. No significant differences with other groups in ACTH challenge. Abused women with MDD often had more comorbid PTSD.
Rinne et al (2002)	Borderline Personality Disorder with (n=24) and without (n=15) sustained childhood abuse, healthy controls (n=11) History of childhood sexual or physical abuse	PTSD Past MDD Schizophrenia, mania, current MDD, and substance abuse were excluded Some patients were medicated	DEX (1.5mg)/CRH(100μg)	Plasma cortisol and ACTH samples were collected every 15 minutes between 3-4:15pm.	Higher plasma cortisol and ACTH levels in abused BPD patients compared to non-abused patients after DEX/CRH challenge

REFERENCE	POPULATION/ TYPE OF INTERPERSONAL TRAUMA	DOCUMENTED DIAGNOSES/ MEDICATIONS	CHALLENGE PARADIGM	HPA AXIS OUTCOME MEASURES	CONCLUSIONS AND REMARKS
De Bellis et al (1994)	Sexually abused girls (n=13), Controls (n=13) Girls were aged 7-15.	Dysthymia No other psychiatric diagnoses were noted. Exclusion criteria included history of substance abuse disorder. All subjects were medication free for at least three weeks.	CRH (1μg/kg)	Plasma ACTH and total and free cortisol were obtained. 24-hour urine cortisol was also obtained.	Sexually abused girls had significantly lower basal and stimulated ACTH responses compared to controls. Total and free plasma cortisol levels and 24-hour urine cortisol were comparable between the two groups.
Kaufman et al (1997)	Abused children with MDD (n=13), Non-abused children with MDD (n=13), Healthy controls (n=13) Abuse is defined as physical or sexual abuse or exposure to extreme marital violence. Males were included and children were aged 7-13.	MDD Exclusion criteria included meeting DSM-III criteria for anorexia nervosa, bulimia nervosa, autism, schizoaffective disorder or schizophrenia. No mention was made about PTSD or other anxiety disorders. All subjects were medication free for at least two weeks.	CRH (1μg/kg)	Plasma cortisol and ACTH samples were collected at -30, -15, and 0, pre-CRH infusion and 14, 30, 60, 90, 120, and 150 post-CRH infusion.	No significant differences were noted between any of the groups for plasma cortisol or ACTH. Abused children with MDD who were experiencing ongoing, chronic adversity (n=7), had higher ACTH responses to CRH than abused children with MDD without ongoing, chronic adversity, non-abused children with MDD, and healthy controls.

B.4. Conclusions

Overall, there is still much work to be done in this area. Much of the research involving IT and the HPA axis has focused primarily on changes in cortisol levels in survivors of CIT. Adult survivors of IT and IPV have been largely ignored in this literature and thus it is not yet possible to draw conclusions about the differential impact of childhood versus adulthood IT on the HPA axis.

Future research must systematically explore the relationships between IT experience, psychiatric sequelae and changes in the HPA axis. Additionally, since most of the previous research has focused primarily on cortisol, it is important to examine specific points of dysregulation by analyzing regulatory hormones and neuropeptides that influence the HPA axis signaling cascade. These include CRH, AVP, ACTH, and β-END, among others. Additional expansion of this research to examine the functional integrity and localization of glucocorticoid, CRH, AVP and β-END receptors would also enhance our understanding of HPA axis functioning in survivors of IT.

While research examining these neuropeptides has been carried out in subjects with exclusively MDD or PTSD, we can only hypothesize what their status will be in survivors of IT with comorbid psychiatric diagnoses resulting from trauma. The complex psychiatric diagnoses that may result from IT make survivors of traumatic interpersonal experiences a very heterogeneous group in which to examine the HPA axis. However, the complexity of their psychiatric profiles should not deter researchers from carrying out research in this population. IT occurring in childhood and adulthood is widespread and common in both industrialized and non-industrialized nations and may account for a significant number of cases of psychiatric stress-related disorders amongst females. The

functional impairment of these women in familial, relational, occupational, and social roles is well documented. An understanding of the biological mechanisms underlying the development of psychiatric syndromes resulting from IT will enable the medical community to treat survivors of IT more appropriately and effectively reduce the suffering and functional impairment endured by both IT survivors and their loved ones.

PURPOSE, OBJECTIVES AND HYPOTHESES OF THE RESEARCH DESCRIBED IN THIS THESIS

I. Purpose

The prevalence rates of both MDD and PTSD are approximately twice as high in women, which has led to a number of hypothesis about the biological, psychosocial, developmental, societal and cultural differences between the sexes that may contribute to these discrepancies. Several authors have suggested that the means by which women cope with stressful life events may partially explain sex differences in prevalence rates of stress disorders such as MDD and PTSD (Breslau et al., 1991; 1998; Kendler et al., 1993; 2002; Kessler et al., 1995; Stein et al., 2000). Cutler and Nolen-Hoeksema (1991) have suggested that up to 35% of the differences between men and women in the prevalence rates of MDD can be explained by higher incidences of childhood sexual abuse in women. It is well accepted that women experience more sexual trauma over their lifetimes but not more trauma in general (Breslau et al., 1991; 1998; Kessler et al., 1995).

While PTSD requires a precipitating traumatic event, the etiology of MDD is far more complex and controversial. Variables such as genetics, stressful life events, predisposing developmental factors, personality traits, cognitive traits, comorbid medical or psychiatric conditions, and psychosocial stressors, among others, have been cited as potential contributing factors in the development of MDD (Kendler et al., 2002; Iosifescu et al., 2004; Farabaugh et al., 2004; Levinson, 2006; Philibert, 2006). In women with histories of IT, it is assumed that their traumatic experiences contribute to the development of MDD, but it is understood that not all women who experience IT go on to develop psychiatric sequelae.

The pathophysiology underlying both MDD and PTSD is currently unknown, but the HPA axis has been a dominant area of research in the pathophysiology of stress disorders for decades. Since the hypothalamus plays a major role in maintaining autonomic and endocrine homeostasis, regulatory mechanisms involving this area of the CNS have been targeted as potential sources of dysregulation in disorders such as MDD and PTSD. In particular, the roles of CRH, cortisol, ACTH, and GRs in the pathogenesis of stress disorders have been active areas of research. Other regulatory mechanisms of the HPA axis have received less attention but may indeed play a role in the pathogenesis of psychiatric symptoms following stressful life events.

The purpose of this research was to compare differences in stress-related symptoms and select HPA axis peptides between three groups of women: (1) depressed women without a history of IT or other stressful life events, (2) depressed women with a history of IT, and (3) healthy controls. Research has demonstrated that women with histories of IT are likely to suffer from more severe psychiatric symptoms as well as have a broader spectrum of psychiatric conditions (Bryer et al., 1987; Bifulco et al., 1991; Pribor and Dinwiddie, 1992; Hall et al., 1993; Young et al., 1997; Campbell, 2002; Kendall-Tackett, 2002). Additionally, we sought to examine HPA axis peptides that had not been previously examined in this particular context. While AVP has been examined in individuals with MDD, it has not been measured in depressed women with histories of traumatic life events. CRH has been exclusively measured in populations with either MDD or PTSD but not in female survivors of IT. Finally, very few studies examining the HPA axis in the context of MDD take into account the potential impact that trauma may have on altering the pathogenesis and pathophysiology underlying stress disorders

resulting from trauma. It is accepted that up to 30% of individuals will not respond to any antidepressant treatment. An increased risk of poor treatment response to antidepressant therapy has been observed in survivors of IT (Browne & Finkelhor, 1986; Boudewyn & Liem, 1995). Thus, since antidepressant therapy works exclusively through biological mechanisms, it seems plausible that differences in the pathophysiology of MDD in women with and without histories of IT may exist.

II. Objectives

1. To investigate potential differences in MDD symptom severity and quality as well as differences in the stress-related symptom severity in depressed women without a history of IT compared to women with histories of IT. This will be accomplished using the Hamilton Depression Rating Scale (HAM-D) and the Trauma Symptom Checklist, respectively. A secondary analysis will be carried out by further subdividing the group of depressed women with IT into those with a current PTSD diagnosis and those without.
2. To investigate possible differences in basal plasma stress hormone concentrations between women with MDD without a history of IT, women with MDD and a history of IT, and female healthy controls. Stress hormones to be measured in this thesis include AVP and CRH. The impact of a PTSD diagnoses in the MDD+IT group on AVP and CRH levels will also be examined.
3. To investigate possible differences in AVP plasma concentrations resulting from CRH pharmacological challenge in depressed women with and without histories

of IT and healthy controls. Again, the impact of a PTSD diagnosis in the MDD+IT group will also be examined.

III. Hypotheses

1. MDD symptom severity is expected to be similar in depressed women with histories of IT compared to depressed women without such histories. However, women in the MDD+IT group are expected to experience more anxiety-related symptoms as a result of their IT experiences. Furthermore, within the MDD+IT group, women with current PTSD diagnoses are expected to have more anxiety-related symptoms that those without current PTSD diagnoses.
2. Basal CRH plasma levels are expected to be similarly elevated in all depressed groups compared to healthy controls. Differences in CRH plasma levels between depressed women with and without IT are not expected.
3. Basal AVP plasma levels are expected to be elevated in depressed groups compared to healthy controls. Since the impact of IT on plasma AVP levels has not been previously investigated, it is not known if IT will affect AVP in humans. However, animal work suggests that AVP levels may be elevated as a result of trauma experiences.
4. CRH pharmacological challenge is expected to lead to more significant increases in plasma AVP concentrations in healthy controls compared to depressed groups. Differences in plasma AVP levels between depressed women with and without IT experiences are not expected.

MATERIALS AND METHODS

I. METHODS 1: RECRUITMENT OF FEMALE SUBJECTS WITH AND WITHOUT MAJOR DEPRESSION FOR PARTICIPATION IN THE DEX/CRH DOUBLE CHALLENGE

A. Initial Contact with Participants

This study was approved by the Health Research Ethics Board Biomedical Panel at the University of Alberta. Women, aged 18-65, were recruited using bulletin board posters as well as local magazine and radio advertising. Volunteers were also recruited by television and radio interviews of Dr. Hegadoren (Principal Investigator of the present study) on news segments for local media outlets, as well as through an article in a local newspaper discussing Dr. Hegadoren's work in women's mental health. In all cases, participation of women struggling with symptoms of MDD and/or healthy volunteers was requested and potential participants were instructed to contact the Research Coordinator for the Women's Health Research Unit (WHRU).

Following contact with the Research Coordinator, initial screening questions were asked in a telephone interview with individual participants. Telephone interview questions included preliminary information about current mental health status, past trauma histories, current medication status, and other current medical conditions. Exclusion criteria for this study are listed in Table 6. Subjects with comorbid psychiatric disorders other than those listed in Table 6 were accepted, since it is well recognized that IT is associated with a number of Axis I and Axis II disorders. At this time, if subjects met appropriate criteria, they were requested to come to the WHRU for a formal interview.

TABLE 6: Exclusion Criteria for the Present Study
• History of Bipolar I Disorder • History of Seasonal Affective Disorder • History of a Psychotic Disorder • Recent Drug or Alcohol Abuse (within last 2 months) • History of a major medical illness • Uncontrolled thyroid dysfunction • Diabetes Mellitus – Type I or II • Currently taking antidepressant medication • Current inhalant or systemic steroid use

B. Diagnostic and Psychological Assessment Tools

The Structured Clinical Interview for Diagnosis (SCID) according to DSM-IV criteria was used to confirm current major depressive episode as well as current and/or past history of other comorbid Axis I disorders. Subjects intended to be healthy volunteers were expected to have no history of MDD or other Axis I and Axis II psychiatric disorders. Furthermore, they were expected to be free of other major medical illnesses and specific medications listed in Table 6. If the woman met criteria for current major depressive episode, further assessment tools were administered:

(1) Hamilton Rating Scale for Depression (HAM-D)

The HAM-D is the most commonly used scale for the assessment of depressive symptoms (Williams, 2001). For this study, the 29-item scale was used; this version includes 12 additional items that cover psychotic symptoms, obsessive/compulsive symptoms, dissociation, atypical symptoms and symptoms associated with seasonal affective disorder in addition to the original 17 items that cover items related to depression and anxiety symptoms (Hamilton, 1960).

(2) Trauma Symptom Checklist (40 items; TSC-40)

The TSC-40 is a 40-item self-report measure which evaluates symptomatology resulting from trauma occurring in either childhood or adulthood (Zlotnick et al., 1996). Subscale scores associated with anxiety, depression, dissociation, sexual abuse trauma index (SATI), sexual problems, and sleep disturbance, as well as a total score, are provided

(3) Sexual Victimization Interview

The sexual victimization interview assesses early sexual trauma by asking questions about the following: (i) nature of the abuse, (ii) age at which the abuse started, (iii) duration of the abuse, (iv) relationship of the victim to the perpetrator, and (v) use of force during the abuse (Russell, 1986). As discussed in the literature review, these elements of sexual trauma have been linked to the severity of sexual abuse and the development of subsequent psychiatric symptomatology.

(4) Physical Abuse Schedule

This subscale of the Child Maltreatment Interview Schedule asks questions about the relationship of the victim to the perpetrator, frequency and duration of physical abuse, age at which abuse occurred, and injuries suffered as a result of abuse (Briere, 1992).

(5) Structured Interview for Disorders of Extreme Stress – Not Otherwise Specified (NOS; SIDES)

The SIDES is a 27 question interview designed to capture symptoms resulting from extreme stress that are not captured in the DSM-IV criteria for PTSD (Pelcovitz et al., 1997). These items are related to alterations in regulation of affect and impulses, alterations in attention or consciousness, alterations in self-perception, and

somatization (Zlotnick and Pearlstein, 1997). This scale was developed specifically for field trials related to the DSM-IV and used to discriminate classic PTSD from complex PTSD (as suggested by Herman, 1992). Insufficient evidence was found to add DESNOS to the DSM-IV classification as a distinct mental disorder.

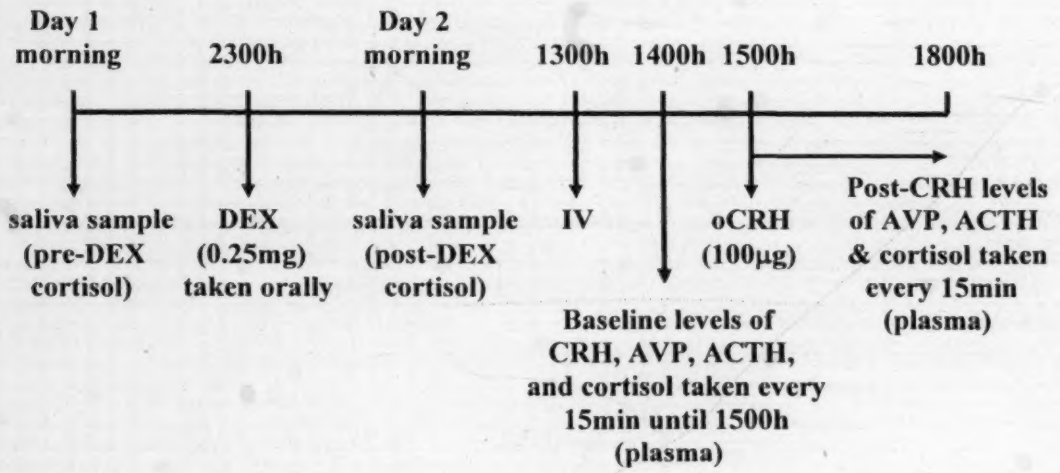
General demographic data and information about current menstrual phase, status, history, and use of oral contraceptives or hormone replacement therapy were obtained. Women in pre-, peri-, and post-menopause were included in the study. Therefore, women on both oral contraceptives and hormone replacement therapy were included in the study. All DEX/CRH double challenges were performed during follicular phase which corresponds to days 6-10 of the menstrual cycle. Finally, before participation in the DEX/CRH double challenge, participants underwent a complete blood count and levels of thyroid stimulating hormone (TSH) were assessed. Since uncontrolled thyroid disease can lead to the development of psychiatric symptoms, TSH was measured to ensure all participants had levels within the normal range.

II. METHODS 2: THE DEX-CRH DOUBLE CHALLENGE

A. General Timeline of the DEX-CRH Double Challenge

The general timeline of the DEX-CRH double challenge is illustrated in Figure 1.

FIGURE 1: Timeline of the DEX/CRH Double Challenge



B. DEX-CRH Double Challenge

Table 7: Chemicals Used in Method 2

Chemicals	Supplier
Human CRH	Merck Biosciences AG (Clinalfa, Switzerland)
0.9% Sodium Chloride	Merck Biosciences AG
Aprotinin	Sigma Chemical Co. (St. Louis, MO, US)

The DEX-CRH double challenge for this study was performed using a modification of the procedure originally described by Bardeleben and Holsboer (1991). On the day of the interview, women were given a kit containing a 0.25mg DEX pill and two Salivettes (devices used for the collection of saliva samples; Sarstedt, Inc., Newton,

NC) to be used in the participant's home once the Research Coordinator confirmed a date for their DEX-CRH double challenge. On day 1 of the double challenge, women were instructed to provide a saliva sample approximately 30 minutes after morning waking for the measurement of basal cortisol levels. We requested that they not eat, drink, or brush their teeth before providing the saliva sample. At 2300 on day 1, women were instructed to ingest the 0.25mg DEX pill. The following morning (day 2 of the challenge), women were asked to provide another saliva sample approximately 30 minutes after waking to assess post-DEX saliva cortisol levels.

On day 2 of the double challenge, women were instructed to come to the WHRU where the CRH infusion test was conducted in a quiet room with the subject resting supine in a recliner chair. Non-stressful movies and music were provided for the subject's entertainment during the 4 hour procedure. A nurse was present during the entire procedure and inserted an intravenous forearm catheter at 1330h to give the subjects 30 minutes to get comfortable. Heart rate and blood pressure were monitored over the course of the entire CRH infusion test using a DINAMAP (Critikon, Norderstedt, Germany). At 1400h, initial blood samples were withdrawn for the measurement of DEX, estradiol, and progesterone. Samples for DEX were taken to confirm that subjects actually ingested the DEX pill, while estradiol and progesterone samples were taken to aid in the confirmation of follicular phase. From 1400h to 1500h, blood sampling was carried out every 15 minutes for cortisol, CRH, AVP, ACTH, and β-END levels. Cortisol, ACTH, and β-END levels were measured and analyzed by other individuals within the WHRU and are not actually part of this thesis. Between sampling the intravenous line was kept patent with normal saline. At 1500h, 100μg of human CRH was reconstituted in 1ml of 0.9% sodium

chloride and delivered to the subject in a bolus over 30 seconds. Blood sampling resumed at 1515 and blood tubes were collected for cortisol, AVP, ACTH, and β-END levels every 15 minutes until 1800h.

All blood samples were collected in pre-chilled 4ml blood tubes with ethylenediaminetetraacetic acid (EDTA) added (Becton and Dickinson and Company, Oakville, ON), except blood samples intended for the measurement of cortisol which were collected in pre-chilled 5ml blood tubes without any additives (Becton and Dickinson and Company, Oakville, ON). Aprotonin, a protease inhibitor, was added to blood tubes collected for the measurement of CRH and β-END. Following collection, blood samples were immediately centrifuged at 3000 rpm at 4°C and the plasma was frozen and stored at -80°C until assay measurement. Saliva samples collected at home by participants were centrifuged at 3000 rpm at 4°C and the saliva was frozen and stored at -80°C until assay measurement.

III. METHODS 3: MEASUREMENT OF AVP

A. Sample Preparation and Extraction of AVP from Plasma

Table 8: Chemicals Used in Method 3

Chemicals	Supplier
Acetonitrile	Fisher Scientific (Fair Lawn, NJ, USA)
AVP ELISA kit	R&D Systems (Minneapolis, MN, USA)
Trifluoroacetic Acid (TFA)	Fisher

Separation (SEP) columns containing 200 mg of C18 (Strata C18-E columns; Phoenix Peptides, Burlingame, CA, USA) were placed on a vacuum manifold (Waters, Milford, Massachusetts, USA) and equilibrated by washing initially with 1ml of

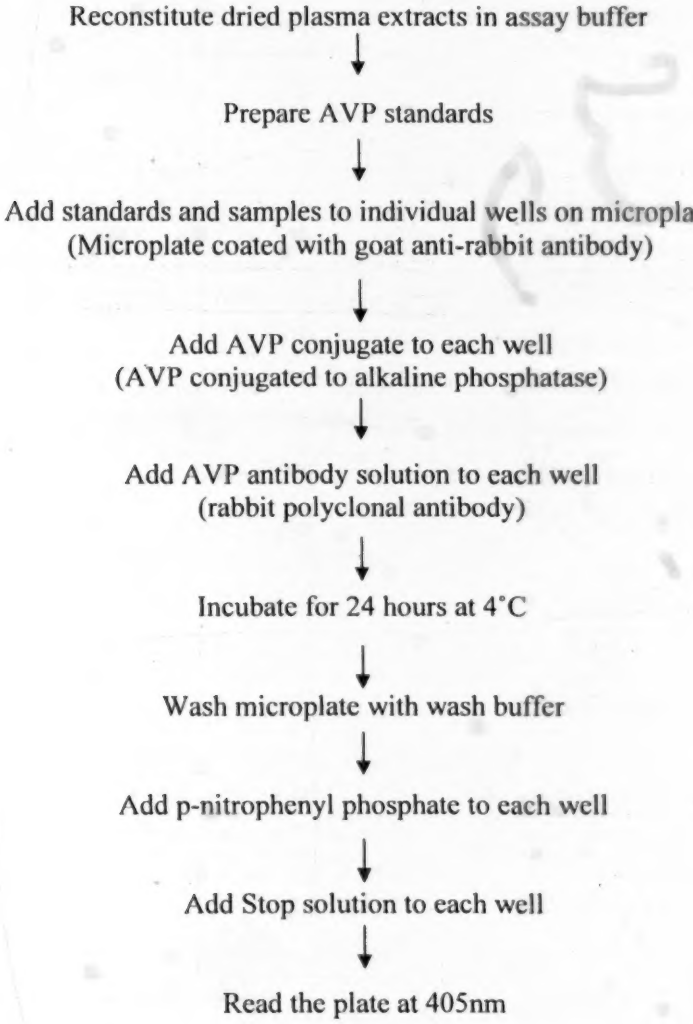
acetonitrile followed by 3 portions of a 3ml 1% TFA solution. Pressure was applied to the columns during the equilibration process.

Plasma samples were acidified with a 1% TFA solution. Equal portions of plasma and TFA solution were added, mixed and the sample was centrifuged at 14000 rpm for 20 minutes at 4°C. Acidified plasma supernatants were then loaded onto the equilibrated C-18 SEP columns. No pressure was applied to the columns for this and subsequent steps. Columns were then washed with 3 portions of a 3ml 1% TFA solution and the eluant was discarded. AVP samples were then eluted with 3ml of a 60:40 mixture of acetonitrile and 1% TFA solution into glass tubes. Samples were then evaporated to dryness using a centrifugal concentrator (Savant, New York, USA).

B. AVP ELISA

AVP levels were determined using an ELISA kit (R&D Systems) based on a competitive binding technique, according to the procedure described in the assay protocol. The protocol is summarized in Figure 2. Microplates were read at 405 nm and with a Power Wave X plate reader (Bio-tek Instruments Inc.) using KC4 software (version 2.7). This ELISA kit has a sensitivity of less than 3.39pg/ml. The intra-assay coefficient of variation is approximately 10.2% while the inter-assay coefficient of variation is 8.5%.

Figure 2: Summary of AVP ELISA Assay Protocol


Reconstitute dried plasma extracts in assay buffer
Prepare AVP standards
Add standards and samples to individual wells on microplate
(Microplate coated with goat anti-rabbit antibody)
Add AVP conjugate to each well
(AVP conjugated to alkaline phosphatase)
Add AVP antibody solution to each well
(rabbit polyclonal antibody)
Incubate for 24 hours at 4°C
Wash microplate with wash buffer
Add p-nitrophenyl phosphate to each well
Add Stop solution to each well
Read the plate at 405nm

IV. METHODS 4: MEASUREMENT OF CRH

A. Sample Preparation and Extraction of CRH from Plasma

Table 9: Chemicals Used in Method 4

Chemicals	Supplier
Acetonitrile	Fisher Scientific (Fair Lawn, NJ, USA)
CRH ^{125}I RIA Kit	Phoenix Peptides (Burlingame, CA, USA)
TFA	Fisher

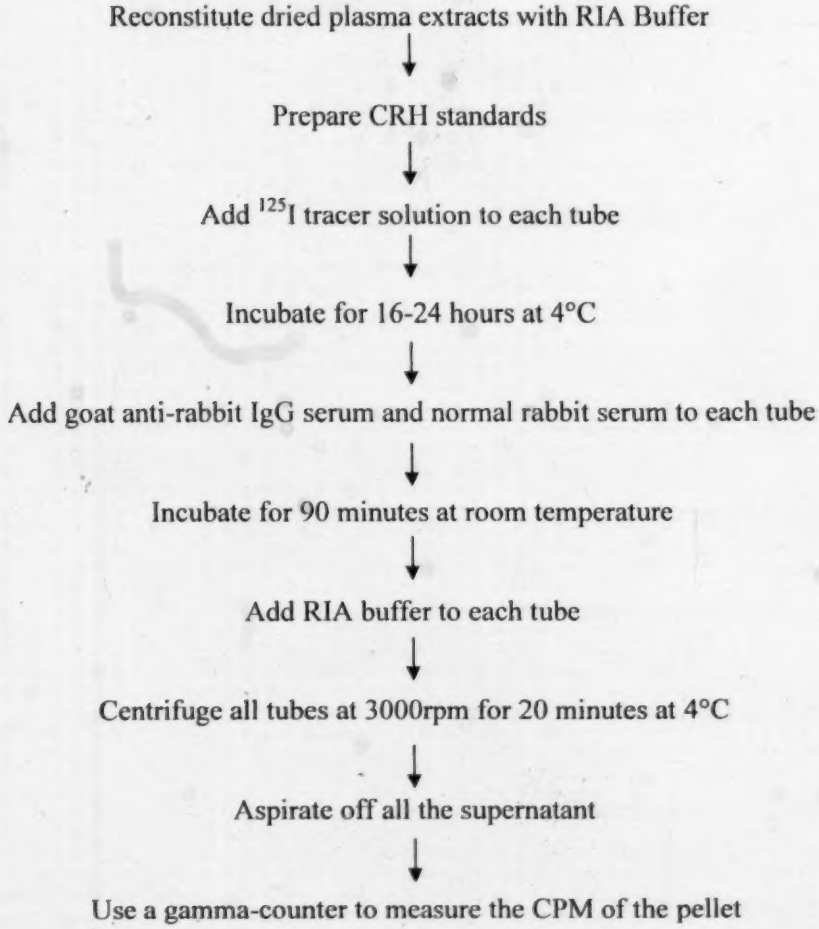
SEP columns containing 200 mg of C18 (Phenomenex C18-E columns; Phoenix Peptides, Burlingame, CA, USA) were placed on a vacuum manifold (Waters, Milford, Massachusetts, USA) and equilibrated by washing initially with 1ml of acetonitrile followed by 3 portions of a 3ml 1%TFA solution. Pressure was applied to the columns during the equilibration process.

Plasma samples were acidified with a 1% TFA solution by mixing equal portions of plasma and TFA solution and the sample were centrifuged at 14000 rpm for 20 minutes at 4˚C. Acidified plasma solutions were then loaded onto the equilibrated C-18 SEP columns. No pressure was applied to the columns for this and subsequent steps. Columns were then washed with 3 portions of a 3ml 1% TFA solution and the eluant was discarded. CRH samples were then eluted with 3ml of a 60:40 mixture of acetonitrile and 1% TFA solution into polystyrene tubes. Samples were then evaporated to dryness using a centrifugal concentrator (Savant, New York, USA).

B. CRH RIA

CRH levels were determined using a ^{125}I RIA kit (Phoenix Peptides, Burlingame, CA, USA) based on a competitive binding technique, according to the procedure described in the assay protocol. This protocol is summarized in Figure 3.

Figure 3: Summary of CRH ^{125}I RIA Protocol


Reconstitute dried plasma extracts with RIA Buffer
Prepare CRH standards
Add 125I tracer solution to each tube
Incubate for 16-24 hours at 4°C
Add goat anti-rabbit IgG serum and normal rabbit serum to each tube
Incubate for 90 minutes at room temperature
Add RIA buffer to each tube
Centrifuge all tubes at 3000rpm for 20 minutes at 4°C
Aspirate off all the supernatant
Use a gamma-counter to measure the CPM of the pellet

V. METHODS 6: MEASUREMENT OF DEXAMETHASONE

To confirm subjects ingested their DEX pills, combined liquid chromatography/mass spectrometry (LC/MS) was used to identify the presence of DEX in plasma samples. DEX levels were not quantified.

SEP columns containing 200 mg of C18 (Strata C18-E columns; Phoenix Peptides, Burlingame, CA, USA) were used to extract DEX from plasma samples. Columns were placed on a vacuum manifold (Waters, Milford, Massachusetts, USA) and equilibrated by washing initially with 1ml of methanol followed by 1ml of deionized water. No pressure was applied to the columns during the equilibration process.

Plasma samples (1ml) were prepared by adding 400µl of methanol. Samples were then vortexed and allowed to sit on ice for 10 minutes. They were then centrifuged for 4 minutes at 10000rpm and the supernatant was loaded onto equilibrated SEP columns. Columns were then washed with 1ml of 5% methanol and DEX was eluted into glass tubes with methanol. Samples were then evaporated to dryness using a centrifugal concentrator (Savant, New York, USA). Samples were stored at -20˚C until further use.

On the day of LC/MS analysis, lyophilized samples were reconstituted in 70µl of solution A (1% formic acid in 2mM of ammonium acetate) and 30µl of solution B (1% formic acid in acetonitrile). Samples were then vortexed and centrifuged at 10000rpm for 10 minutes. The supernatant was then transferred to HPLC vials and stored in the dark at 4˚C.

The LC/MS was set up using the following specifications and parameters:

Column: Symmetry C18 (150x2.1mm; Waters)

Guard: Symmetry C18 (Waters)

Temperature: 30°C

Flow: 0.2ml/min

Injection volume: 20µl where available; 10µl for all others

Mobile phase A: 1% formic acid in 2mM ammonium acetate

Mobile phase B: 1% formic acid in acetonitrile

Gradient: Samples were eluted using 70% phase A to 30% phase B

Samples were injected onto the column and ionized by positive electrospray (Cone voltage = 30kV). DEX was identified by locating a peak with an ion mass of 393.2 daltons.

VI. METHODS 7: MEASUREMENT OF ESTRADIOL AND PROGESTERONE

Estradiol and progesterone were measured using ELISA kits (ALPCO Diagnostics, Salem, NH, USA) based on a competitive binding technique according to the procedure described in the respective assay protocols. Assay protocols for estradiol and progesterone are summarized in Figures 4 and 5 respectively. Microplates were read at 450 nm for both estradiol and progesterone with a Power Wave X plate reader (Bio-tek Instruments Inc.) using KC4 software (version 2.7).

Figure 4: Summary of Estradiol ELISA Assay Protocol

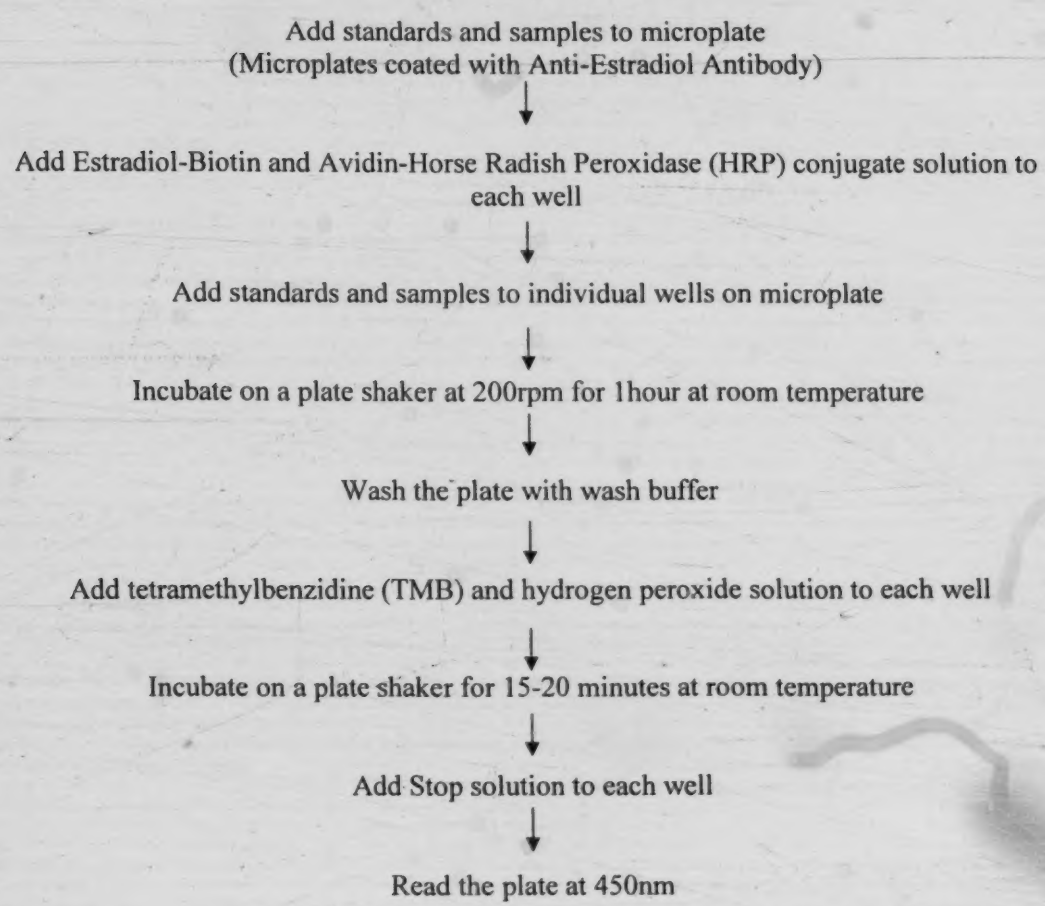
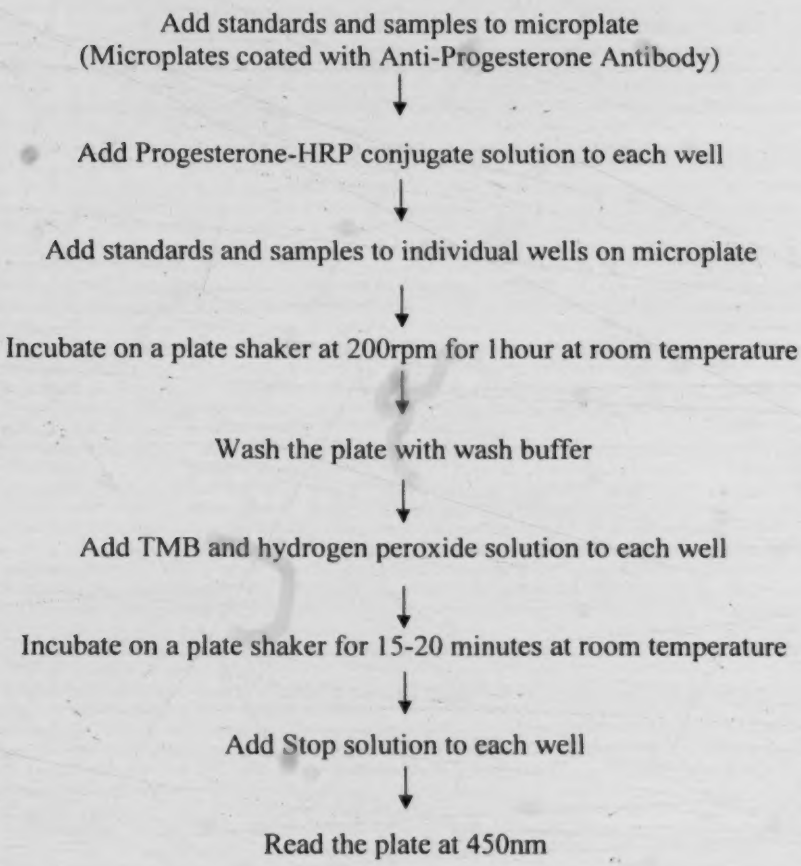

Add standards and samples to microplate
(Microplates coated with Anti-Estradiol Antibody)
Add Estradiol-Biotin and Avidin-Horse Radish Peroxidase (HRP) conjugate solution to each well
Add standards and samples to individual wells on microplate
Incubate on a plate shaker at 200rpm for 1hour at room temperature
Wash the plate with wash buffer
Add tetramethylbenzidine (TMB) and hydrogen peroxide solution to each well
Incubate on a plate shaker for 15-20 minutes at room temperature
Add Stop solution to each well
Read the plate at 450nm

Figure 5: Summary of Progesterone ELISA Assay Protocol


Add standards and samples to microplate
(Microplates coated with Anti-Progesterone Antibody)
Add Progesterone-HRP conjugate solution to each well
Add standards and samples to individual wells on microplate
Incubate on a plate shaker at 200rpm for 1hour at room temperature
Wash the plate with wash buffer
Add TMB and hydrogen peroxide solution to each well
Incubate on a plate shaker for 15-20 minutes at room temperature
Add Stop solution to each well
Read the plate at 450nm

VII. STATISTICAL METHODS

Data for AVP and CRH were expressed as mean ± standard deviation (SD) and tested for normality of distribution to determine whether further analysis would be carried out using parametric or non-parametric (Kruskal-Wallis) statistics. HAM-D and TSC-40 scores and subscales were expressed as mean ± SD and then compared for group differences using the Kruskal-Wallis test, followed by the Mann-Whitney test.

The Kolmogorov-Smirnov test showed that AVP levels were normally distributed at each time point over the course of the DEX-CRH challenge. Repeated measures analysis of variance (RM-ANOVA) was used to assess the effect of time on plasma levels of AVP. Basal values for AVP were calculated by averaging AVP values at -30 and -15min for each individual and one-way ANOVA with least significant difference (LSD) post-hoc analysis was used to assess group differences. Peak AVP and ΔAVP (peak AVP-basal AVP) levels resulting from CRH challenge were also calculated and one-way ANOVA with LSD post-hoc analysis was used to test differences between groups. Areas under the curve (AUC) for AVP concentration versus time were calculated using the trapezoidal rule and one-way ANOVA with LSD post-hoc analysis was used to assess group differences. The level of significance for all analyses was set at $p<0.05$.

Basal CRH levels were not normally distributed at each time point before the CRH injection as determined by the Kolmogorov-Smirnov test, and therefore non-parametric statistics were used to analyze these data sets. The Kruskal-Wallis test was used to identify group differences followed by Mann-Whitney post-hoc analysis.

ANALYSIS

I. DEMOGRAPHIC DATA AND SAMPLE CHARACTERISTICS

Table 10: Summary of Sample Characteristics

	Healthy Controls (n=17)	MDD without history of IT (n=19)	MDD with history of IT (n=23)
Age	40±11	43±13	44±10
Hormone Status			
Follicular	12	11	14
Hysterectomy	0	1	1
Perimenopausal	0	1	6
Postmenopausal	5	5	4
Use of Oral Hormones			
None	11	13	16
Oral Contraceptives	4	2	3
HRT Progestin-like	1	1	3
HRT Estrogen-like	1	1	2
HRT Both	0	1	1
Comorbid Anxiety Disorders			
Generalized Anxiety Disorder	0	7	8
Obsessive Compulsive Disorder	0	0	3
Panic Disorder	0	6	7
Social Phobia	0	2	3
Trauma Symptoms			
PTSD	0	0	13
DESNOS-current	0	0	0
DESNOS-subthreshold	0	0	15
DESNOS-past	0	0	13

A. Introduction

Sample characteristics for each group are summarized in Table 10. Subjects were age- and hormone status-matched between groups and no significant differences in age were noted between the groups.

Over the course of the DEX-CRH double challenge, a number of technical issues were encountered that prevented some subjects from continuing in the study. These

included but were not limited to: inability to set up a date to do the DEX-CRH challenge that was mutually acceptable for both subjects and lab staff, improperly followed instructions around ingestion of the DEX pill, blood withdrawal issues, and significant discomfort or pain experienced during the blood withdrawal process. Subjects that did not participate in the DEX-CRH challenge for any issue were withdrawn from the study and their interview and ratings scale data were not included in the final analysis.

B. Healthy Controls

Overall, 20 healthy controls fit the inclusion criteria for the current study. Subjects that were found to have a positive psychiatric history during the initial interview process using the SCID were excluded from the study and were not included in any of the analyses.

For the final analysis, post-menopausal subjects were over-represented in the healthy control group and thus, 3 subjects were randomly removed and not included in the final analysis. HAM-D testing was not carried out for the healthy control group and the SCID was used as the sole determinant for the presence or absence of depressive symptoms in this group. The TSC-40 was administered to all groups in the study, including healthy controls. While healthy controls did report experiencing some symptoms listed within the TSC-40 (summarized in Table 12), these symptoms were not clinically significant for any single individual.

C. MDD Without History of IT

Of the 20 subjects with MDD without a history of IT who participated in the DEX-CRH challenge, only 19 were included in the final analysis. One subject was removed from analysis because it was found that she had a history of bipolar disorder which is one of the exclusion criteria for the current study. The other subject was removed from this group because it was discovered, after measuring her estradiol and progesterone levels, that she had already entered the ovulatory phase and was no longer in follicular phase of her menstrual cycle.

D. MDD With History of IT

Initially, 27 subjects with MDD and a history of IT participated in the DEX-CRH challenge. Of this group, only 25 were used in the final analysis. One subject was withdrawn because it was discovered that she had already entered the ovulatory phase of her menstrual cycle upon measurement of estradiol and progesterone. Another subject was withdrawn due to an unexpected conflict between project staff during the course of her DEX-CRH challenge. This conflict served as an unexpected psychosocial stressor for the subject and therefore, may have acted as a confounding variable for her set of data.

The psychiatric diversity within the group of subjects with MDD and IT histories presented a number of interesting challenges for the data analysis. Initially, analyses were to be carried out by grouping all survivors of IT into a single group of trauma survivors. As outlined in the literature review, this approach has been employed by several studies examining survivors of IT where individuals are classified on the basis of experience rather than diagnosis. However, studies examining the HPA axis in survivors of motor

vehicle crashes, natural disasters, and other types of trauma have found that a PTSD diagnosis has a significant impact on the functioning of the HPA axis (see literature review). While all subjects in this group had experienced some form of IT over the course of their lifetimes, not all subjects met full criteria for current PTSD as defined by the DSM-IV. Many subjects that did not meet criteria for current PTSD met criteria for past or subthreshold DESNOS. Overall, all subjects met criteria for past, current, or subthreshold PTSD or DESNOS. While several studies have explored the relationship between PTSD and the HPA axis in survivors of IT (see literature review), no studies have examined the impact of a DESNOS diagnosis on the HPA axis. Since none of our subjects in this group had met current criteria for DESNOS, but rather had experienced either full or subthreshold criteria for DESNOS in the past, it was not possible to create separate PTSD and DESNOS groupings

In response to these issues, two separate sets of analyses were run. The first set of analyses did not subdivide the IT group and were run using the following groups: (1) Healthy controls, (2) MDD-history of IT, and (3) MDD+history of IT. The second set split the IT trauma group on the basis of whether subjects had current PTSD diagnoses: (1) Healthy controls, (2) MDD-history of IT (2) MDD+history of IT-PTSD and (4) MDD+history of IT+PTSD. Healthy control and MDD-history of IT groups remained the same in both sets of analyses

E. Symptom Severity Scales

E.1 Grouped on the Basis of Presence/Absence of IT History

Since healthy controls were not administered the HAM-D, they will not be discussed further in the HAM-D discussion. HAM-D ratings scores are summarized in Table 11. There were no significant differences between the MDD with and without history of IT groups on the 17-item HAM-D. However, for the both the 21- and 29-item HAM-D, scores were significantly higher in depressed individuals with histories of IT compared to those without IT histories. This suggests that while there appears to be no significant difference in the severity of depression and anxiety symptoms assessed by the 17-item scale, there does appear to be significantly more atypical depressive symptoms in the IT history group, covered by the 29-item HAM-D.

Table 11: HAM-D Rating Scale – MDD With or Without History of IT

	Healthy Controls (n=17) Mean±SEM	**MDD without history of IT (n=19) Mean±SEM**	**MDD with history of IT (n=23) Mean±SEM**
HAM-D (Total Items: 1 to 17)	-	16.35±1.35	19.78±1.35
HAM-D (Total Items: 1 to 21)	-	17.65±1.41	22.65±1.48*
HAM-D (Total Items: 1 to 29)	-	23.29±1.89	31.22±1.97**

(*) = $p<0.05$, compared to MDD without history of IT; (**) = $p<0.01$, compared to MDD without history of IT

The differences in psychiatric sequelae between depressed individuals with and without histories of IT were further confirmed by results from the TSC-40 rating scale (summarized in Table 12). As expected, both MDD groups had significantly greater scores on dissociation, anxiety, depression, SATI, sleep disturbance, and sexual problem

subscales as well has higher total scores compared to healthy controls ($p<0.001$). When comparing the two depressed groups, those with IT histories had significantly greater dissociation ($p<0.05$), SATI ($p<0.01$), sleep disturbance ($p<0.01$), and total ($p<0.01$) scores compared to those without trauma histories. There were no significant differences in anxiety, depression, and sexual problem subscales between the two groups.

Finally it is important to note that there were differences in the number of participants who participated in HAM-D rating scales and TSC-40 scales. For three participants (1 healthy control, and 2 MDD subjects with IT histories), completed TSC-40 scales were not available in their files and it is therefore unknown whether each subject was actually given a copy of the TSC-40 to complete for the study.

Table 12: Trauma Symptom Checklist 40 – MDD With or Without History of IT

	Healthy Controls (n=17) Mean±SEM	**MDD without history of IT (n=19) Mean±SEM**	**MDD with history of IT (n=23) Mean±SEM**
Dissociation Total Items: 7, 14, 16, 25, 31, 38	1.17±0.35	5.18±0.70*	7.61±0.87* #
Anxiety Total Items: 1, 4, 10, 16, 21, 27, 32, 39	2.00±0.35	6.24±0.84*	8.26±0.93*
Depression Total Items: 2, 3, 9, 15, 19, 20, 26, 33, 37	2.94±0.67	13.88±0.79*	16.17±1.12*
SATI Total Items: 5, 7, 13, 21, 25, 29, 31	0.94±0.27	5.65±0.75*	8.52±0.73* +
Sleep Disturbance Total Items: 2, 8, 13, 19, 22, 28	2.88±0.41	9.88±0.87*	12.78±0.67* +
Sexual Problems Total Items: 5, 9, 11, 17, 23, 29, 35, 40	1.33±0.42	6.94±0.79*	8.04±1.07*
TSC Total Score Total Items 1-40.	10.06±1.35	44.41±2.30*	56.17±3.29* +

(*) = $p<0.001$, compared to healthy controls; (+) = $p<0.01$, compared to MDD without history of IT; (#) = $p<0.05$, compared to MDD without history of IT

E.2 Grouped on the Basis of Presence/Absence of PTSD in IT Group

The MDD+IT group was divided into those with and without current PTSD and a secondary analysis was performed for HAM-D scores. Data for this analysis are summarized in Table 13. Overall, there were no significant differences between subjects with MDD and histories of IT compared to those without MDD with no previous history of trauma on any of the HAM-D scales. When both groups were compared to subjects who had experienced IT with comorbid MDD and PTSD, significant differences were observed. Compared to the MDD without history of IT group, the MDD+IT+PTSD group had significantly higher scores on the 17-item ($p<0.05$), 21-item ($p<0.01$), and 29-item ($p<0.01$) HAM-D scales. When compared to the group of depressed subjects who did not have current PTSD as a result of their IT experiences, the MDD+IT+PTSD group had significantly higher scores on the 17-item ($p<0.05$), and 21-item ($p<0.05$) HAM-D scales but not the 29-item HAM-D. These results suggest that depressed women with current PTSD as a result of IT experiences have more frequent or more severe depressive symptoms than both depressed women without histories of IT and women with histories of IT who do not have current PTSD diagnoses.

Table 13: HAM-D Rating Scale – IT Group Divided into MDD Subjects With and Without PTSD

	Healthy Controls (n=17) Mean±SD	MDD without history of IT (n=19) Mean±SD	MDD+IT-PTSD (n=9) Mean±SD	MDD+IT +PTSD (n=14) Mean±SD
HAM-D (Total Items: 1 to 17)	-	16.35±1.35	17.20±4.10	22.08±4.75$^{*\#}$
HAM-D (Total Items: 1 to 21)	-	17.65±1.41	20.20±4.69	25.46±4.88$^{+\#}$
HAM-D (Total Items: 1 to 29)	-	23.29±1.89	29.78±9.21	33.38±3.82^{+}

(*) = $p<0.05$, compared to MDD without history of IT; (+) = $p<0.01$, compared to MDD without history of IT; (#) = $p<0.05$, compared to MDD+IT-PTSD

A secondary analysis was also performed for TSC-40 scores when the MDD+IT group was divided into those with and without current PTSD. Data for this analysis are summarized in Table 14. For the TSC-40, all three depressed groups had significantly higher total scores ($p<0.001$) as well as higher scores on dissociation, anxiety, depression, SATI, sleep disturbance, and sexual problem subscales ($p<0.001$ for all) compared to healthy controls. When comparing the three depressed groups, depressed subjects with histories of IT without current PTSD had higher scores on SATI ($p<0.05$) and sleep disturbance ($p<0.05$) subscales as well as higher total scores compared to women with MDD without a history of trauma ($p<0.05$). Traumatized women with both MDD and PTSD had significantly higher scores on dissociation ($p<0.05$), depression ($p<0.05$), SATI ($p<0.01$), and sleep disturbance ($p<0.05$) subscales, as well as higher total TSC-40 scores compared to depressed women without a history of IT. There were no significant differences between depressed women with histories of IT with and without current PTSD diagnoses.

Table 14: Trauma Symptom Checklist 40 – IT Group Divided into MDD Subjects With and Without PTSD

	Healthy Controls (n=17) Mean±SD	MDD without history of IT (n=19) Mean±SD	MDD +IT -PTSD (n=9) Mean±SD	MDD+IT+PTSD (n=14) Mean±SD
Dissociation Total Items: 7, 14, 16, 25, 31, 38	1.17±0.35	5.18±0.70*	7.89±4.17*	8.67±4.12*+
Anxiety Total Items: 1, 4, 10, 16, 21, 27, 32, 39	2.00±0.35	6.24±0.84*	8.11±5.11*	8.42±3.70*
Depression Total Items: 2, 3, 9, 15, 19, 20, 26, 33, 37	2.94±0.67	13.88±0.79*	16.67±4.15*	17.00±4.47*+
SATI Total Items: 5, 7, 13, 21, 25, 29, 31	0.94±0.27	5.65±0.75*	8.11±2.85*+	9.58±3.20*#
Sleep Disturbance Total Items: 2, 8, 13, 19, 22, 28	2.88±0.41	9.88±0.87*	13.22±1.79*+	13.17±3.01*+
Sexual Problems Total Items: 5, 9, 11, 17, 23, 29, 35, 40	1.33±0.42	6.94±0.79*	8.78±4.82*	8.83±4.80*
TSC Total Score Total Items 1-40	10.06±1.35	44.41±2.30*	57.78±14.25*+	59.33±10.42*#

(*) = $p<0.001$, compared to healthy controls; (+) = $p<0.05$, compared to MDD without history of IT; (#) = $p<0.01$, compared to MDD without history of IT

II. AVP

A. AVP Analysis with all IT Survivors Grouped Together Regardless of PTSD Diagnosis

No significant differences in basal AVP levels were noted between any group [$F(2,59)=1.204$, $p<0.31$]. These data are summarized in Figure 6 and Table 15.

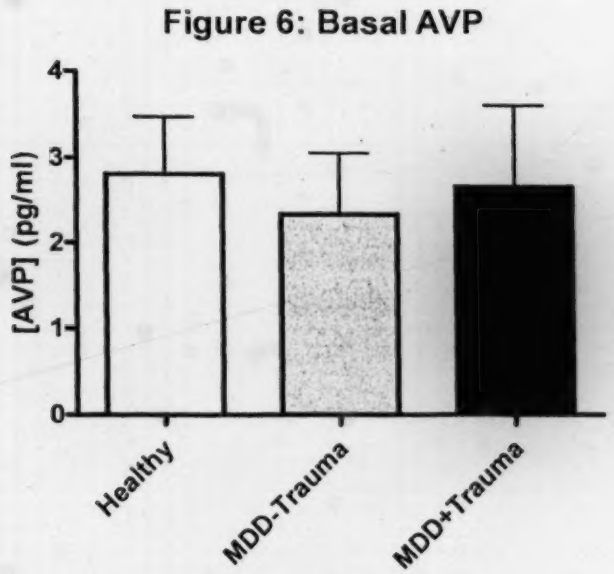


Figure 6: Basal AVP levels calculated by taking the mean of values obtained at -30 and -15 minutes. Results are expressed as mean ± SD. No significant differences were observed between groups.

While assessing for the effect of time on AVP levels, Mauchley's test of sphericity showed that sphericity could not be assumed and the Greenhouse-Geisser correction was used to calculate degrees of freedom in the F tests. The Greenhouse-Geisser corrected RM-ANOVA did not reveal a significant effect of time on plasma AVP

concentrations [$F(3.75,52)=1.932$, $p<0.12$]. Time course data for each group is shown in Figure 7. Note that in Figure 7, the AVP concentration at time=0 is the basal concentration while that observed at time point 1 is 15 minutes after CRH infusion. Blood samples to measure AVP levels were taken every 15 minutes after CRH infusion.

Figure 7: AVP Time Course

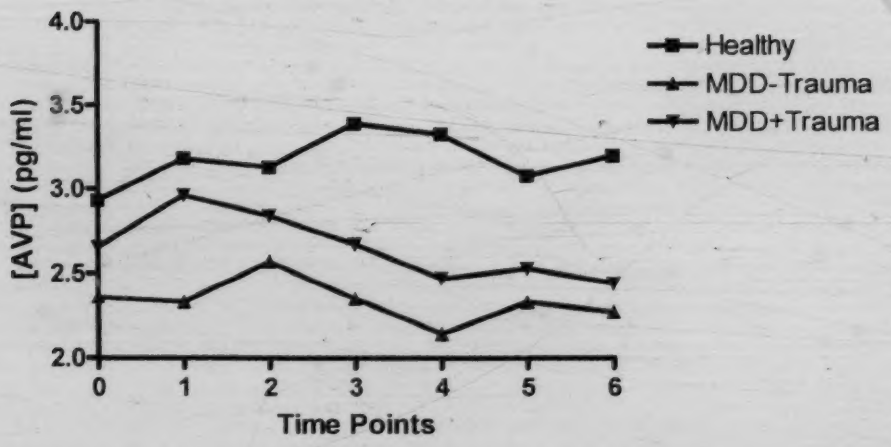


Figure 7: Time course data for AVP over the course of the DEX-CRH challenge. Time 0 represents basal plasma AVP levels while every point thereafter represents 15 minute intervals following IV CRH (100μg) infusion. No significant differences were observed between groups.

While there was no significant impact of time between groups, ANOVA revealed significant differences in AUC [$F(2,52)=4.49$, $p<0.05$). LSD post-hoc analysis showed that the MDD without history of IT group had a significantly smaller AUC compared to healthy controls ($p<0.005$). Further, the MDD+IT group showed a trend to decreased AUC compared to healthy controls ($p<0.075$). There were no significant differences between the two depressed groups. AUC data is summarized in Table 15 and Figure 8.

Figure 8: AVP AUC

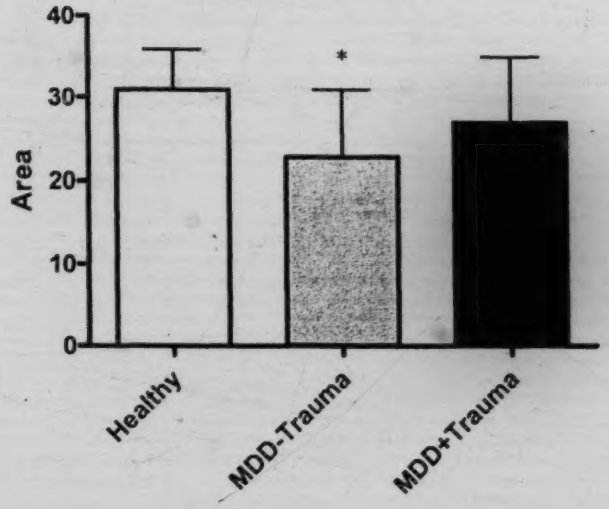


Figure 8: AVP AUC over the course of the DEX-CRH challenge. Results are expressed as mean ± SD. AVP AUC for the MDD-IT group was significantly decreased compared to the healthy control group (= $p<0.05$ compared to healthy controls).*

Finally, there were no significant group differences in peak ([$F(2,52)=2.074$, $p<0.14$]; summarized in Figure 9 and Table 15) or ΔAVP values ([$F(2,52)=0.798$, $p<0.46$]; summarized in Figure 10 and Table 15). However, there was a trend towards decreased peak AVP levels in the MDD-trauma group compared to healthy controls ($p<0.06$).

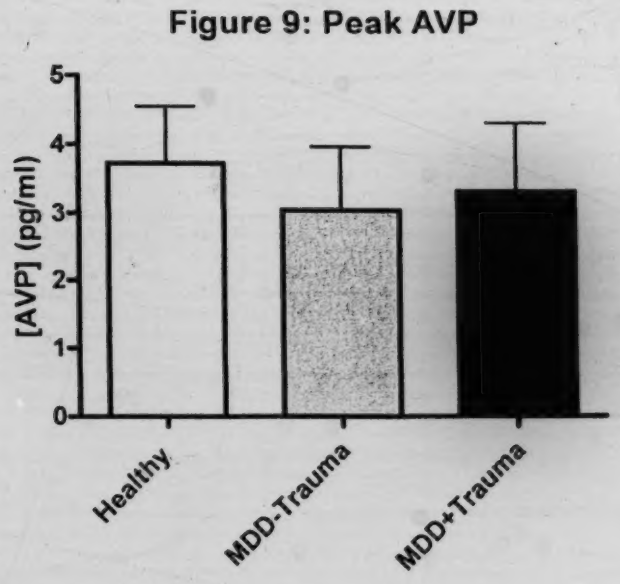


Figure 9: Peak plasma AVP levels following CRH challenge. Results are expressed as mean ± SD. No significant differences were observed between groups.

Figure 10: Delta AVP

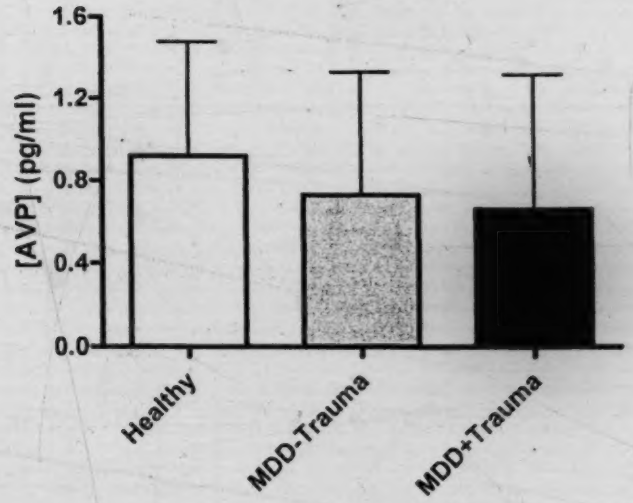


Figure 10: Change in plasma AVP levels following CRH infusion. Results are expressed as mean ± SD. No significant differences were observed between groups.

Table 15: Summary of AVP Data with IT Survivors Grouped Together Regardless of PTSD Diagnosis

	Basal AVP (pg/ml) Mean±SD	Peak AVP (pg/ml) Mean±SD	ΔAVP (pg/ml) Mean±SD	AUC (pg/ml/min) Mean±SD
Healthy (n=17)	2.81±0.67	3.72±0.83	0.92±0.56	30.95±4.90
MDD-Trauma (n=19)	2.34±0.72	3.04±0.92	0.73±0.60	22.86±8.10*
MDD+Trauma (n=23)	2.60±0.95	3.32±0.99	0.66±0.66	26.93±7.96

p<0.005 compared to healthy controls

B. AVP Analysis with IT Group Split into MDD+PTSD and MDD-PTSD

No significant differences in basal AVP levels were noted between any group [$F(2,59)=1.228$, $p<0.31$]. However, there was a trend towards decreased basal AVP levels in the MDD without a history of IT compared to healthy controls. These data are summarized in Figure 11 and Table 16.

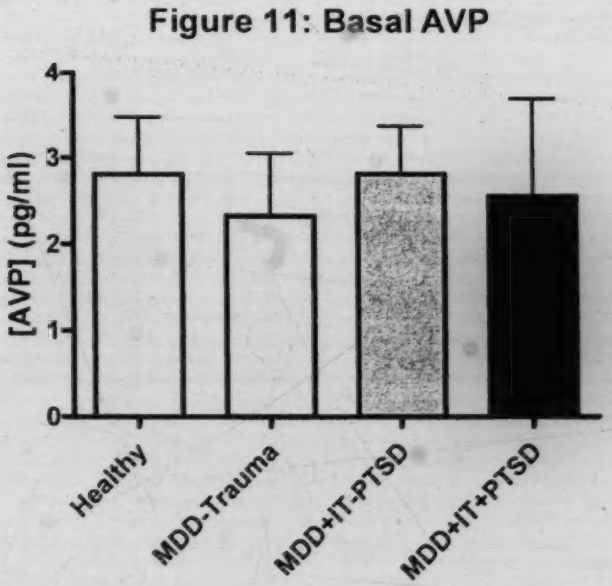


Figure 11: Basal AVP levels calculated by taking the mean of values obtained at -30 and -15 minutes with the MDD+IT group re-classified on the presence or absence of PTSD. Results are expressed as mean ± SD. No significant differences were observed between groups.

While assessing for the effect of time on AVP levels, Mauchley's test of sphericity showed that sphericity could not be assumed and the Greenhouse-Geisser correction was used to calculate degrees of freedom in the F tests. The Greenhouse-Geisser corrected RM-ANOVA did not reveal a significant effect of time on plasma AVP

concentrations [$F(3.67,52)=2.204$, $p<0.08$]. Time course data for each group are shown in Figure 12. Note that in Figure 12, the AVP concentration at time=0 is the basal concentration while that observed at time point 1, is 15 minutes after CRH infusion. AVP levels were taken every 15 minutes after CRH infusion.

Figure 12: AVP Time Course

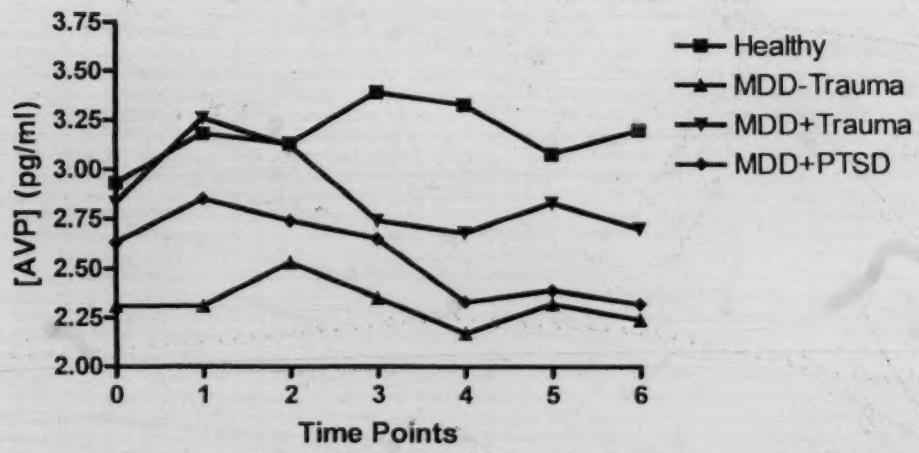


Figure 12: Time course data for AVP over the course of the DEX-CRH challenge with the MDD+IT group re-classified on the presence or absence of PTSD . Time 0 represents basal plasma AVP levels while every point thereafter represents 15 minute intervals following IV CRH (100μg) infusion. No significant differences were observed between groups.

While there was no significant impact of time between groups, ANOVA revealed significant differences in AUC [$F(3,52)=3.43$, $p<0.05$). LSD post-hoc analysis showed that the MDD without history of IT group had a significantly smaller AUC compared to healthy controls ($p<0.005$). Further, the MDD+IT+PTSD group showed a trend to decreased AUC compared to healthy controls ($p<0.075$). The MDD-IT group also showed a trend to decreased AVP levels compared to the MDD+IT group ($p<0.09$).

There were no significant differences between the two trauma groups. AUC data are summarized in Table 16 and Figure 13.

Figure 13: AVP AUC

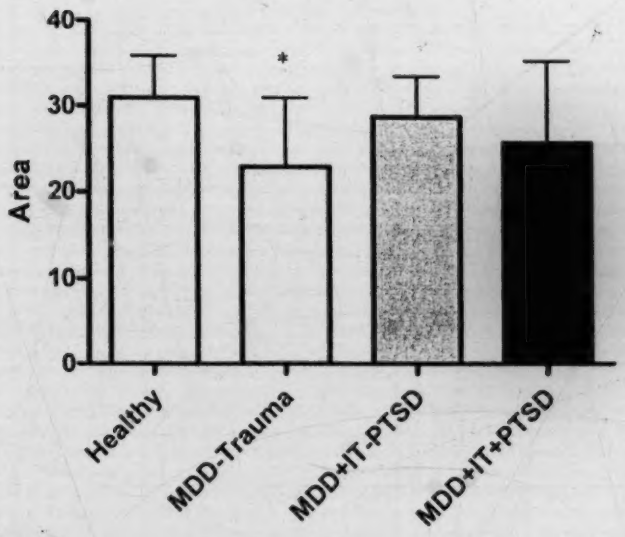


Figure 13: AVP AUC over the course of the DEX-CRH challenge with the MDD+IT group re-classified on the presence of absence of PTSD. Results are expressed as mean ± SD. AVP AUC for the MDD-IT group was significantly decreased compared to the healthy control group (= $p<0.05$ compared to healthy controls).*

Finally, there were no significant group differences in peak ([$F(3,52)=1.669$, $p<0.19$]; summarized in Figure 14 and Table 16) or ΔAVP values ([$F(3,52)=0.581$, $p<0.63$]; summarized in Figure 15 and Table 16). However, LSD post-hoc analysis revealed decreased peak AVP levels in the MDD-trauma group compared to healthy controls ($p<0.05$).

Figure 14: Peak AVP

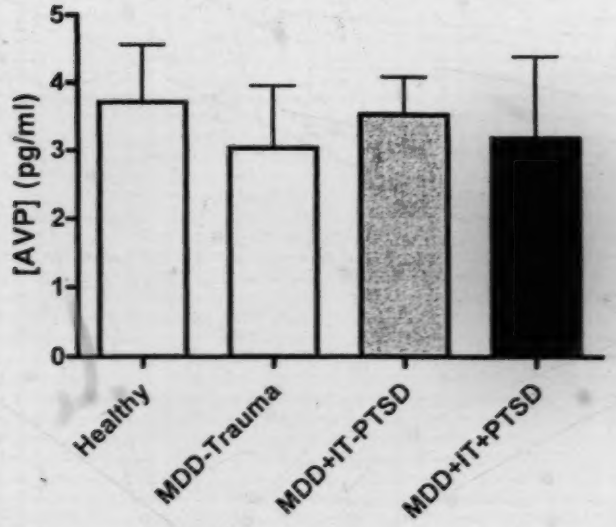


Figure 14: Peak plasma AVP levels following CRH challenge with the MDD+IT group re-classified on the basis of presence of absence of PTSD. Results are expressed as mean ± SD. No significant differences were observed between groups.

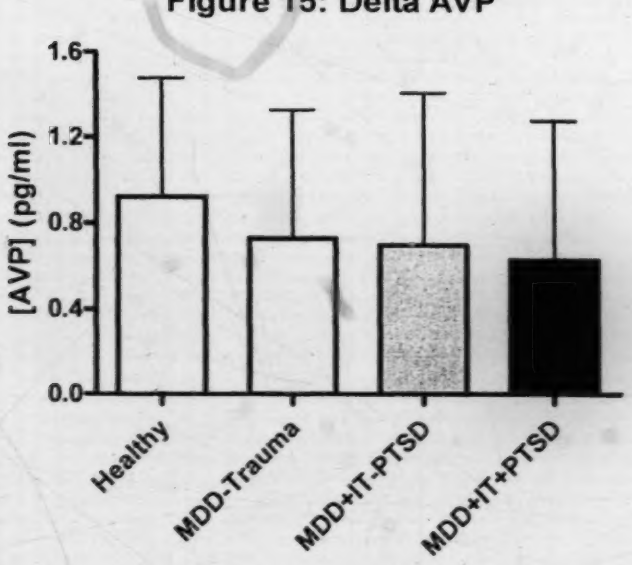


Figure 15: Change in plasma AVP levels following CRH infusion with the MDD+IT group re-classified on the basis of presence or absence of PTSD. Results are expressed as mean ± SD. No significant differences were observed between groups.

Table 16: Summary of AVP Data with IT Group Split into MDD+PTSD and MDD-PTSD

	Basal AVP (pg/ml) Mean±SD	Peak AVP (pg/ml) Mean±SD	ΔAVP (pg/ml) Mean±SD	AUC (pg/ml/min) Mean±SD
Healthy	2.81±0.67	3.72±0.83	0.92±0.56	30.95±4.90
MDD-Trauma	2.33±0.72	3.04±0.92*	0.70±0.71	22.86±8.10*
MDD+IT-PTSD	2.82±0.56	3.53±0.55	0.63±0.65	28.70±4.78
MDD+IT+PTSD	2.56±1.14	3.19±1.19	0.63±0.65	25.75±9.54

p<0.005 compared to healthy controls

III. CRH

A. CRH Analysis with all IT Survivors Grouped Together Regardless of PTSD Diagnosis

No significant differences in basal plasma CRH levels were identified between groups. Data are summarized in Table 17 and Figure 16.

Figure 16: Basal CRH

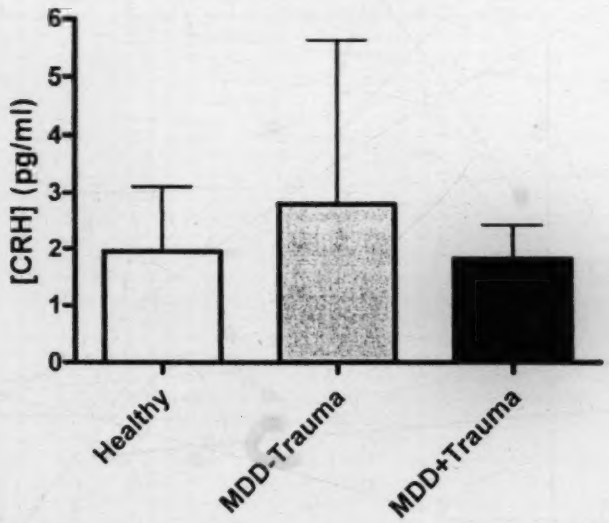


Figure 16: Basal CRH levels calculated by taking the mean of values obtained at -30 and -15 minutes. Results are expressed as mean ± SD. No significant differences were observed between groups.

Table 17: Summary of CRH Data with all IT Survivors Grouped Together Regardless of PTSD Diagnosis

	Basal CRH (pg/ml) Mean±SD
Healthy (n=16)	1.95±1.16
MDD-Trauma (n=19)	2.81±2.83
MDD+IT (n=21)	1.82±0.61

B. CRH Analysis with IT Group Split into MDD+PTSD and MDD-PTSD

No significant differences in basal plasma CRH levels were identified between groups. Data are summarized in Table 18 and Figure 17.

Figure 17: Basal CRH

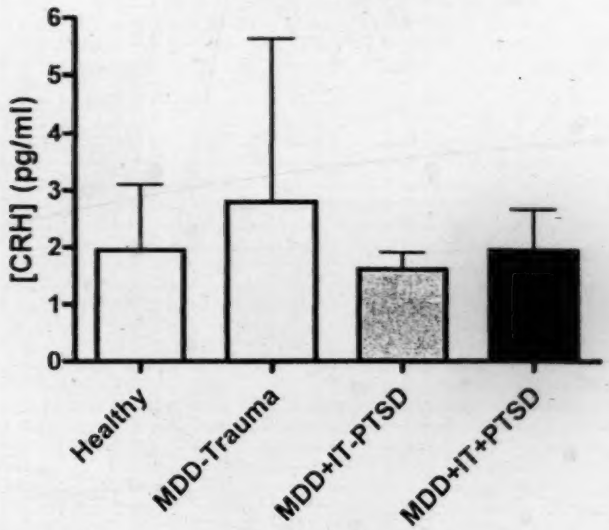


Figure 17: Basal CRH levels calculated by taking the mean of values obtained at -30 and -15 minutes with the MDD+IT group re-classified on the basis of presence or absence of PTSD. No significant differences were observed between groups.

Table 18: CRH Analysis with IT Group Split into MDD+PTSD and MDD-PTSD

	Basal CRH (pg/ml) Mean±SD
Healthy (n=16)	1.95±1.16
MDD-Trauma (n=19)	2.81±2.83
MDD+IT-PTSD (n=8)	1.61±0.30
MDD+IT+PTSD (n=13)	1.95±0.72

DISCUSSION

I. STUDY OVERVIEW AND CHALLENGES

A. Technical Challenges

This thesis is based entirely on data collected from human participants over a 4 year period from 2001 to 2005. Over the course of the current study, there were a number of unexpected issues that were encountered and subsequently resolved. While 93 women were recruited and interviewed for the study, only 65 actually underwent a DEX-CRH double challenge. Of the participants that were recruited and did not undergo blood collection, approximately 25% did not show up for their scheduled challenges while the rest appeared for their scheduled appointment but due to technical issues, blood samples could not be obtained.

The IV insertion and blood collection aspects of the study proved to be very technically demanding and required a high level of expertise from our nursing staff. Early in the study, many participants were lost because we were unable to obtain blood and since we were measuring hormones associated with the HPA axis, a stress response system in the body, we were reluctant to aggressively pursue blood samples. Further, several subjects experienced pain or discomfort over the course of the challenge and in some cases, blood withdrawal was stopped prematurely to ensure the comfort of the patient and quality of the data.

B. Classification of the Depressed Group With Histories of IT

As was described in the literature review, there are a number of complex psychiatric outcomes that can result from IT experiences. Overall, women with histories

of IT tend to be a heterogeneous group, presenting a number of ways in which they can be classified. Many women who have experienced IT, regardless of the dimensions of trauma, have comorbid presentations of both MDD and PTSD, along with other comorbid diagnoses. Since previous research has shown that differential changes in the HPA axis may be observed in MDD and PTSD (Young, 2006; Pariante, 2006; Gillespie and Nemeroff, 2006; Rasmusson et al., 2003; Shea et al., 2005; Seckl and Meaney, 2006; de Kloet et al., 2006), this presents classification problems in the examination of HPA axis changes in IT survivors. Potential confounding variables within this group when examining the HPA axis include, but are not limited to, duration and severity of IT, period of the lifespan in which trauma occurred, number of IT experiences across the lifespan, types of different psychiatric diagnoses, comorbid physical or psychiatric conditions, medications, and time elapsed since trauma occurred. While it is important to capture the spectrum of distress experienced by IT survivors, the psychiatric and experiential plurality demostrated by this population presents challenges in both recruitment and investigation of biological variables. Broad inclusion criteria will introduce too many confounding variables into a study of this particular population, while criteria that are too restrictive may lead to recruitment issues.

Previous researchers examining the HPA axis in populations of IT survivors have generally dealt with this issue by controlling for either type of IT experience (i.e. childhood IT, adult sexual assault, IPV) or psychiatric diagnoses (MDD or PTSD). In studies where psychiatric diagnoses were uncontrolled, subjects were usually recruited on the basis of whether they had MDD or PTSD and the other diagnosis was simply a

comorbid condition in some participants (along with other Axis I or Axis II diagnoses). These studies were summarized in the literature review in Tables 3-5.

Unfortunately, past research examining the HPA axis in IT survivors was not helpful in elucidating a classification scheme of IT survivors for the current study. Therefore, we opted to run two separate sets of analyses where the IT survivors were analyzed as a whole group and then a secondary analysis was run, where the MDD+IT group was subdivided on the basis of the presence or absence of current PTSD. While this seems like a straightforward approach, all individuals without current PTSD had either subthreshold symptoms of either PTSD or DESNOS suggesting symptomatic similarities between the two groups. Additionally, due to the small sample size, we were unable to examine the impact of dimensions of the type (physical, sexual or both; adulthood, childhood, or both), severity and duration of IT on the HPA axis. Future research must address these issues. While it may seem counterintuitive to conduct biological research in psychiatrically and experientially homogeneous groups of IT survivors when the population as a whole seems fundamentally diverse, it will only be possible to understand more complex outcomes resulting from IT if we have an understanding of how each potential construct may contribute to changes in the HPA axis and other neural networks involved in mood, anxiety, memory, and stress response.

II. RATING SCALES

A. Hamilton Depression Rating Scale

Since HAM-D interviews were not performed with healthy controls, comparisons were only made between depressed groups. Using the 17-item HAM-D, there were no

significant differences in scores between the MDD-IT and MDD+IT groups. This implies that the severity of depression and number of typical depressive symptoms was approximately equal between the two groups.

Differences between the two groups emerged using the 21- and 29-item HAM-D scales. Using the 21-item scale, the MDD+IT group had significantly higher scores than the MDD-IT group. Therefore, the MDD+IT group experienced more depersonalization, paranoid, and obsessive-compulsive symptoms than the MDD-IT group. As with the 21-item HAM-D, the MDD+IT group also had higher scores on the 29-item scale. This suggests that the MDD+IT group experienced more atypical depressive symptoms such as weight gain, increased appetite, carbohydrate craving, hypersomnia, and social withdrawal.

Further divergence using the HAM-D scales occurred when the MDD+IT group was separated into individuals with and without current PTSD resulting from their IT experiences. The MDD+IT+PTSD group had significantly higher scores on the 17-item HAM-D compared to MDD+IT-PTSD and MDD-IT groups. There were no differences on the 17-item HAM-D between the MDD+IT-PTSD and MDD-IT groups. It is unknown whether the MDD+IT+PTSD group had higher scores due to more severe depressive episodes or symptom overlap between MDD and PTSD contributing to more severe distress for individuals with both conditions.

Using the 21-item HAM-D, the MDD+IT+PTSD group also had higher scores compared to MDD+IT-PTSD and MDD-IT groups. Again, there were no differences between the MDD+IT-PTSD and MDD-IT groups. As assessed by the 29-item HAM-D, the MDD+IT+PTSD group had more atypical depressive symptoms than the MDD-IT

group but not the MDD+IT-PTSD group. Further there were no differences in atypical symptoms between the MDD+IT-PTSD and MDD-IT groups. While the HAM-D only seeks information about typical and atypical symptoms associated with MDD, these findings support earlier data that suggest that individuals with comorbid MDD and PTSD have more severe distress than individuals with either condition alone (Shalev et al., 1998; Blanchard et al., 1998).

B. Trauma Symptom Checklist 40

Using the TSC-40, depressed women with IT histories had more dissociative symptoms, sleep disturbance and sexual abuse-associated symptoms (SATI subscale) as well as higher total scores compared to depressed women without IT histories. This was expected as dissociation and sleep disturbance are part of symptom clusters observed within PTSD diagnostic criteria. Furthermore, no individual within the MDD-IT group had experienced sexual trauma, and therefore they were not expected to have symptoms associated with such experiences. Finally, while it is expected that the MDD+IT group would have more anxiety symptoms compared to the MDD-IT group, there were no significant differences between the two groups. However, these data may be confounded by the fact that individuals with comorbid anxiety disorders other than PTSD were included in both the MDD-IT and MDD+IT groups (summarized in Table 12).

When compared to healthy controls, the MDD-IT group had a significantly elevated SATI scores. Examination of this subscale reveals that specific items in the SATI subscale are not specific to symptoms resulting from sexual trauma. This includes items "sexual problems" and "memory problems" which can occur as a result of MDD

itself as well as items such as "nightmares" and "feelings that things are unreal" which are open to interpretation and not exclusive to sexual trauma.

Separation of the MDD+IT group into those with and without current PTSD demonstrated that individuals with current PTSD had more dissociative symptoms compared to the MDD-IT group. The MDD+IT-PTSD group did not have significantly different dissociative symptoms than either the MDD-IT or the MDD+IT+PTSD groups. This indicates that while the MDD+IT-PTSD group has some dissociative symptoms, they are not as severe as those experienced in the MDD+IT+PTSD group. The depressed groups with IT experiences with and without current PTSD diagnoses had significantly higher scores on sleep disturbance and SATI subscales as well as higher total scores compared to the depressed group without IT histories.

C. Comparison of the HAM-D and Depression Subscale of the TSC-40

The depression subscale on the TSC-40 captures most of the symptoms assessed using the 17-item HAM-D. Therefore, similar results should be expected using either scale. In the current study, we found no significant differences between MDD-IT and MDD+IT groups using the 17-item HAM-D and the depression subscale of the TSC-40. When the MDD+IT group was split into individuals with and without current PTSD diagnoses, the MDD+IT+PTSD group had higher scores than the MDD-IT group on both the 17-item HAM-D and the depression subscale of the TSC-40. Further, there were no significant differences between MDD-IT and MDD+IT-PTSD groups on either scale. These findings indicate that the TSC-40 depression subscale is a good alternative to the

17-item HAM-D where self-report measures are preferred as a means of assessing typical depressive symptoms.

III. CRH

A. Basal CRH Measurements in Depressed Women With and Without Histories of IT

No significant differences in plasma CRH levels were observed between depressed women with and without histories of IT in the current study. There were also no differences between the two depressed groups and healthy controls. Furthermore, depressed individuals who had experienced IT but did not have a current PTSD diagnoses did not have significantly different plasma CRH levels than those who had a current PTSD diagnosis as a result of their IT experiences. Plasma CRH levels were not measured following the IV infusion of CRH since an exogenous 100μg infusion of CRH leads to markedly elevated of plasma CRH that mask any endogenous changes that may be occurring.

While it has been generally accepted that CRH levels are elevated in MDD (Nemeroff et al., 1984; Arato et al., 1986; 1989; Banki et al., 1992; Widerlov et al., 1988; Risch et al., 1991; De Bellis et al., 1993; Catalan et al., 1998; Galard et al., 2002), other studies have suggested that this may not be the case (Kling et al., 1991; Geracioti et al., 1992; Molchan et al., 1993; Pitts et al., 1995; Geracioti et al., 1997). In particular, Geracioti and colleagues (1992; 1997) have provided compelling evidence that single point measurements of CRH may not accurately reflect changes within the HPA axis. These studies also observed initial rises in CRH immediately following lumbar puncture,

rapidly fluctuating levels of CRH, and a brief half-life. Additionally, Geracioti et al. (1997) found that CSF CRH did not correlate with plasma ACTH and cortisol levels. Therefore, they suggest that CSF CRH is primarily extrahypothalamic in origin.

Initial rises in CRH observed by Geracioti and colleagues (1992; 1997) likely result from the pain and psychological distress caused by lumbar puncture with either a syringe or indwelling catheter. Lumbar punctures procedures are acutely invasive, painful and distressing to most participants and therefore, the common use of this procedure to assess CRH levels cannot be ruled out as a pseudo-stress challenge in both MDD and healthy volunteers. The finding that CRH levels decline over the course of serial sampling using an indwelling catheter supports this suggestion (Geracioti et al., 1992; 1997). In studies that found increased plasma CRH levels in MDD, single point measurements were also used (Catalan et al., 1998; Galard et al., 2002). For the current study, catheters were inserted into the arms of participants approximately 45 minutes before initial blood samples were withdrawn. Therefore, initial rises in CRH caused by the discomfort of needle or catheter insertion likely would not be observed if they indeed exist.

Elevated CRH levels in CSF have also been observed in PTSD (Bremner et al., 1997; Baker et al., 1999). However, these two studies also used single point measurements of CRH in CSF obtained by lumbar puncture. The current study did not find elevations in plasma levels of CRH in subjects in either depressed women with histories of IT or in depressed women with current PTSD diagnoses. No studies have looked at plasma CRH levels in individuals with PTSD.

The use of lumbar puncture and CSF sampling could not be justified for the current study since there are a number of ethical issues around the use of this procedure in research settings. Of particular importance, is the invasiveness of lumbar puncture and how individuals with MDD and/or stress-related psychiatric illness may respond to this procedure physically, biochemically and psychologically. As discussed in the literature review, CRH is intimately connected to pain pathways in the body, and therefore, techniques such as lumbar puncture and blood sampling may cause an initial rise in CRH that may be influenced by the mental health status and trauma history of affected individuals.

Future research must address inconsistencies between serial sampling and single point measurements of CRH, particularly in individuals with stress-related psychiatric sequelae. Also, correlations between plasma, CSF and CNS concentrations of CRH have not been adequately resolved. Presently, it is not possible to correlate CNS concentrations of CRH with those measured in the periphery in living human subjects. Furthermore, it is not possible to differentiate between hypothalamic and extrahypothalamic contributions to peripheral concentrations of CRH. Advances in imaging techniques such as PET may address some of these issues.

IV. AVP

A. Baseline Levels of AVP in Depressed Women with and Without Histories of IT

The current study found that basal plasma AVP levels did not differ between depressed groups with or without IT and healthy controls. These results are consistent with a number of studies that have shown no significant differences between individuals

with depression and healthy controls (Raskind et al., 1979; Gjerris et al., 1985; Sörenson et al., 1985; Ritchie et al., 1991; Inder et al., 1997). Past studies did not specify whether individuals with depression had histories of traumatic life events which may precipitate stress disorders. Unlike past work in this area, the current study employed multiple measurements of plasma AVP over an hour and therefore expands upon previous literature that employed single plasma measurements of AVP. By taking multiple baseline measurements of AVP, we were able to confirm that plasma AVP levels remained relatively constant over the period before CRH challenge.

There were no significant differences in plasma AVP levels between depressed women with a history of IT and those without such histories. Secondary analysis where the MDD+IT group was separated into subjects with current PTSD and those without a current PTSD diagnosis also showed no significant differences in baseline AVP levels between the two trauma groups. This is a new finding since there were no published reports examining plasma AVP concentrations in individuals with PTSD diagnoses or histories of IT.

Much of the research examining changes in AVP synthesis, storage, and release has been carried out in animals. While animal studies have suggested that chronic stress may lead to increased synthesis and release of AVP during chronic psychosocial and immobilization stress (Hauger et al., 1990; Bertini and Kiss, 1991; De Goeji et al., 1992; Whitnall, 1989; Scott and Dinan, 1998), it is difficult to extrapolate these findings to predict what might happen to basal plasma levels of AVP in human subjects with psychiatric symptomatology associated with stress disorders. Much more invasive techniques can be used in animals to determine the localization and synthesis of AVP as

well as to isolate anterior and posterior pituitary sources of AVP contributing to concentrations measured in plasma. Furthermore, while beyond the scope of this thesis, the validity of animal stress models to study neurobiological changes in psychiatric disorders such as MDD and PTSD has been repeatedly critiqued and analyzed (Cohen and Zohar, 2004; Anisman and Matheson, 2005; Henn and Vollmayr, 2005; Pryce et al., 2005; Siegmund and Wotjak, 2006). Thus, while animal studies have suggested baseline modifications of AVP in the PVN and median eminence as a result of chronic stress, these findings have not yet been supported by clinical studies examining specific psychiatric disorders such as MDD and PTSD where acute and/or chronic stress have contributed to the development of psychiatric sequelae.

B. AVP Levels Following CRH Challenge in Depressed Women with and Without IT

Repeated measures analysis did not show a significant effect of time on AVP levels and therefore it can be inferred that CRH infusion does not significantly elevate plasma AVP levels. However, the current study is limited by small sample sizes, and due to the large variation in AVP levels between individuals, may not have sufficient power to identify time effects resulting from CRH infusion. Further, there were no significant differences between depressed groups with and without histories of IT and healthy controls using repeated measures.

Time course studies examining the effect of pharmacological challenges on cortisol or other HPA axis-related peptides like ACTH or β-END frequently express the results as AUC rather than using repeated measures statistical analyses. Therefore, we

have employed both methods of analysis in this study. By calculating the AUC for each individual, it was observed that the depressed group without a history of IT had a smaller AUC than healthy controls ($p<0.005$). Further, the MDD+IT group showed a trend to decreased AUC compared to healthy controls ($p<0.075$). No significant differences in AUC were identified when the MDD+IT group was separated into those with and without current PTSD. There were also no significant differences noted between the traumatized and non-traumatized depressed groups.

Since AUC represents a cumulative measure of AVP over a period of time, it is possible that this value has greater power to identify differences between groups. Additionally, the absence of significant differences in basal plasma AVP levels between healthy controls and the two depressed groups suggests that differences between groups may emerge after CRH infusion. Unfortunately, the effect of CRH infusion on plasma AVP levels has not been well studied in human or animal studies. In the current study, CRH infusion was used as a pharmacological stress challenge. Previous studies have shown increased plasma AVP levels in humans during social isolation and confinement (Maillet et al., 1993) and during exposure to psychological stressors (Meyerhoff et al., 1990). However, the neural pathways activated during these two studies that contributed to elevated AVP levels may be entirely different than pathways activated by intravenous CRH infusion. One study suggested that CRH infusion alone does not elevate plasma AVP, but that CRH infusion in the presence of an osmotic stimulus did lead to rises in plasma AVP levels (Yamada et al., 1989). In the current study, when each group was examined separately, AVP levels rose in response to CRH infusion in healthy controls. This was not observed in the MDD-IT or MDD+IT groups. Therefore, impaired

regulation of AVP release by elevated CRH levels may represent a marker in pathophysiology in MDD.

While a synergistic role for CRH and AVP in the activation of the HPA axis cascade has been established, interactions between these two peptides have not been well studied. Research has exclusively focused on the effects of AVP and CRH in regulating the release of ACTH under conditions of acute and chronic stress and in stress-free environments. As discussed in the literature review, this includes examining both levels of AVP and CRH in stressful and stress-free conditions as well as examining changes with V_{1b} and CRH_1 receptors occurring as a result of acute and chronic stress. However, since CRH and AVP act synergistically, each has the potential to regulate the release of the other from the hypothalamus. In particular, CRH pathways in brain regions other than the hypothalamus may have the ability to affect AVP release from the PVN during acute and chronic stress.

The current study suggests a possible role for CRH in the regulation of AVP release. The mechanism by which this occurs is unknown. Since intravenous CRH infusions cross the blood-brain barrier and interact with CRH receptors diffusely throughout the brain, it is likely that AVP release may be modified by CRH via extrahypothalamic sites that have stimulatory inputs into the PVN of the hypothalamus. In particular, inputs from the cortex, amygdala and ventrolateral medulla as well as ascending projections from autonomic areas of the brain stem which are rich in CRH receptors may play a role in regulating AVP release from the PVN (Ruggiero et al., 1999; Kirby et al., 2000; Valentino and Van Bockstaele, 2002). These regions in particular have been shown to be involved in HPA axis regulation (Herman et al., 1996; 2003; 2005).

V. SUMMARY OF KEY FINDINGS

A. Differences in Psychiatric Profiles in Depressed Women with and without Histories of IT

In the present study, it was observed that depressed women with histories of IT experience more atypical symptoms of MDD than women without such histories. They also experience more dissociative, sexual abuse related symptoms, and sleep disturbance than depressed women without histories of IT. Additionally, every participant with a history of IT also had subthreshold or current PTSD diagnoses. These findings support suggestions that depressed women with histories of IT may have more complex psychiatric profiles than depressed women without such histories. As a result, they may require more aggressive psychiatric interventions since comorbidity has been associated with higher levels of functional impairment (Shalev et al., 1998; Blanchard et al., 1998) and higher rates of treatment resistance (Brady et al., 2000).

Since many women with histories of IT will initially present to health clinics and physicians seeking help for MDD, this study supports the need for these practitioners to inquire about IT experiences occurring in either childhood or adulthood. While some women may be reluctant to talk about such experiences initially, patient education around the potential psychiatric consequences of IT and inquiries around such histories may lead to disclosure of IT histories during future appointments. Identification of such individuals may allow health practitioners to more effectively identify comorbid psychiatric conditions in these individuals as well as formulate more effective treatment strategies.

B. CRH in Depressed Women with and without Histories of IT

The current study found no differences in basal plasma CRH levels between controls and depressed women with and without histories of IT. These findings are supported by other studies that have not observed differences in CSF and plasma CRH in subjects with MDD (Kling et al., 1991; Geracioti et al., 1992; Molchan et al., 1993; Pitts et al., 1995; Geracioti et al., 1997). Conversely, hypersecretion of CRH has been frequently described in both MDD (Nemeroff et al., 1984; Arato et al., 1986; 1989; Banki et al., 1992; Widerlov et al., 1988; Risch et al., 1991; De Bellis et al., 1993; Catalan et al., 1998; Galard et al., 2002) and PTSD (Bremner et al., 1997; Baker et al., 1999). It is unknown why there is inconsistency in this literature, but addressing some of the issues raised earlier in the discussion around single- versus multiple-point sampling, the use of CSF versus plasma CRH, and the origin of CRH in samples drawn from peripheral sources may clarify this literature.

C. AVP in Depressed Women with and without Histories of IT

The current study did not observe differences in basal plasma AVP concentrations between healthy controls and either of the two depressed groups. In response to CRH challenge, the depressed group without a history of IT had a decreased AVP AUC compared to healthy controls. Depressed women with histories of IT showed a trend towards decreased AUC compared to healthy controls, but this finding did not reach significance. There appeared to be no differences between depressed women with and without histories of IT. This is a new finding since CRH challenge of AVP has not been

previously used in human subjects and therefore, future work must delineate a mechanism by which this results in decreased AVP AUC for subjects with MDD.

Several studies, described in the literature review, have examined AVP levels in individuals with MDD but this literature has been inconsistent. Neither basal nor challenged AVP levels have been examined in a population with a history of IT or PTSD previously. While all subjects in the present study had current MDD diagnoses, we did not find a significant effect of subthreshold or current PTSD diagnoses resulting from IT on either basal or CRH-challenged AVP concentrations. This is a new finding and should be examined in future studies investigating AVP levels in individuals with PTSD resulting from IT as well as other types of traumatic life events.

VI. CONCLUSION

A wide spectrum of psychiatric outcomes can occur in response to IT. As a result, female survivors of IT are a diverse and heterogeneous group, and thus controlling variables to examine potential biological markers of dysfunction can be challenging. In women with histories of severe, prolonged and/or repeated IT, resulting psychiatric symptoms may not fit into the strict diagnostic constructs described in the DSM-IV. This issue may be resolved in future research by taking a symptoms-based approach to the pathophysiology of stress disorders. The heterogeneity of symptoms observed in female survivors of IT suggests that multiple pathways in the brain may be affected. Therefore, a symptomatic approach to examining pathophysiology may be more insightful than examination on the basis of Axis I or II groupings since female survivors of IT often have complex psychiatric histories.

While it is tempting to dismiss biological research in female survivors of IT due to methodological challenges in controlling potential confounding variables, this is still an important area of research. It is commonly believed that only a minority of individuals who experience IT go on to have psychiatric issues. There is, however, a disproportionate number of psychiatric patients who have experienced IT. It has been estimated that up to 2/3 of adult psychiatric patients have histories of IT (Beck and van der Kolk, 1987; Bryer et al., 1987; Briere and Zaidi, 1989; Mueser et al., 2004; McHugo et al., 2005). Furthermore, treatment resistance has been observed in survivors of IT, particularly in those with complex psychiatric profiles (Mancini et al., 1995; Kaplan and Klinetob, 2000; Schneider et al., 2007). For these individuals, psychotherapy combined with antidepressant therapies are likely more effective in the treatment of psychiatric sequelae associated with IT (Stein et al., 2000; Martsolf and Draucker, 2005; Bisson and Andrew, 2007). Thus, it is extremely important that physicians inquire about trauma histories to determine the best course of treatment for individual patients.

With regard to the role of the HPA axis in the pathophysiology of stress disorders, there are still many unanswered questions. HPA axis dysregulation has been observed in both MDD (Young, 2006; Pariante, 2006; Gillespie and Nemeroff, 2006) and PTSD (Rasmusson et al., 2003; Shea et al., 2005; Seckl and Meaney, 2006; de Kloet et al., 2006). Problems with methodology and confounding variables within populations have made the implications of some results unclear. While the HPA axis has been a primary focus of research in the pathophysiology of MDD, PTSD, and other stress-related psychiatric illness, the implications of dysregulation within the HPA axis on mood, anxiety, memory and cognition have not been clarified. Furthermore, there is still much

to learn about the regulation of the HPA axis and how changes within this network can influence other important pathways within the CNS involved in the regulation of mood and anxiety.

It has been suggested that modifications in the regulation of glucocorticoid release due to stressful life events could potentially lead to long-term changes in neural plasticity in areas of the CNS involved in the regulation of mood and anxiety, resulting in psychiatric symptoms (Pearce and Yamamoto, 1993; McKay and Cidlowski, 1998; Chrousos and Kino, 2007). However, there is insufficient evidence to delineate specific behaviors associated with stress-related psychiatric illness resulting from altered glucocorticoid release in the context of this hypothesis.

An alternative hypothesis has revolved around potential CRH dysregulation in stress-related psychiatric illness. While the HPA axis is frequently implicated in CRH dysregulation in both MDD and depression, CRH dysregulation in extrahypothalamic pathways seems more plausible. Rodent models suggest an increase in anxiety-related behaviors in the presence of increased extrahypothalamic CRH (Dunn and Berridge, 1990; Butler and Nemeroff, 1990; Koob et al., 1993; Young and Liberzon, 2002). Further, it has been hypothesized that hypothalamic CRH release occurs in response to physiological stress, while CRH release from the central nucleus of the amygdala occurs in response to fear-related behaviors (Makino et al., 1999) and emotionally significant stimuli (Merali et al., 2003). Conversely, the behavioral implications of CRH dysregulation within the HPA axis have not been clearly delineated. While the involvement of extrahypothalamic CRH dysregulation in the production of symptoms associated with stress-related psychiatric illness is a promising area of research, there is

still much to learn about the behavioral impact of changes in CRH neurotransmission in human brain and how these changes may result in psychiatric symptoms associated with MDD and/or PTSD.

REFERENCES

Aardal-Eriksson E, Eriksson TE, Thorell LH: Salivary cortisol, posttraumatic stress symptoms, and general health in the acute phase and during 9-month follow-up. Biol Psychiatry 50(12):986-93, 2001

Ackerman PT, Newton JE, McPherson WB, Jones JG, Dykman RA: Prevalence of post traumatic stress disorder and other psychiatric diagnoses in three groups of abused children (sexual, physical, and both). Child Abuse Negl 22(8):759-74, 1998

Aguilera G: Regulation of pituitary ACTH secretion during chronic stress. Front Neuroendocrinol 15(4):321-50, 1994

Aguilera G, Harwood JP, Wilson JX, Morell J, Brown JH, Catt KJ: Mechanisms of action of corticotropin-releasing factor and other regulators of corticotropin release in rat pituitary cells. J Biol Chem 258(13):8039-45, 1983

Aguilera G, Nikodemova M, Wynn PC, Catt KJ: Corticotropin releasing hormone receptors: two decades later. Peptides 25(3):319-29, 2004

Akana SF, Dallman MF, Bradbury MJ, Scribner KA, Strack AM, Walker CD: Feedback and facilitation in the adrenocortical system: unmasking facilitation by partial inhibition of the glucocorticoid response to prior stress. Endocrinology 131(1):57-68, 1992

Allen JG, Huntoon J, Evans RB: A self-report measure to screen for trauma history and its application to women in inpatient treatment for trauma-related disorders. Bull Menninger Clin 63(3):429-42, 1999

Altemus M, Cloitre M, Dhabhar FS: Enhanced cellular immune response in women with PTSD related to childhood abuse. Am J Psychiatry 160(9):1705-7, 2003

Amar AF and Gennaro S: Dating violence in college women: Associated physical injury, healthcare usage, and mental health symptoms. Nursing Research *54(3), 2005*

Anand A, Shekhar A: Brain imaging studies in mood and anxiety disorders: special emphasis on the amygdala. Ann N Y Acad Sci 985:370-88, 2003

Anand KJ, Coskun V, Thrivikraman KV, Nemeroff CB, Plotsky PM: Long-term behavioral effects of repetitive pain in neonatal rat pups. Physiol Behav 66(4):627-37, 1999

Andreski P, Chilcoat H, Breslau N: Post-traumatic stress disorder and somatization symptoms: a prospective study. Psychiatry Res 79(2):131-8, 1998

Angst J, Gamma A, Gastpar M, Lepine JP, Mendlewicz J, Tylee A; Depression Research in European Society Study: Gender differences in depression. Epidemiological findings from the European DEPRES I and II studies. Eur Arch Psychiatry Clin Neurosci 252(5):201-9, 2002

Anisman H, Matheson K: Stress, depression, and anhedonia: caveats concerning animal models. Neurosci Biobehav Rev 29(4-5):525-46, 2005

Anisman H, Zaharia MD, Meaney MJ, Merali Z: Do early-life events permanently alter behavioral and hormonal responses to stressors? Int J Dev Neurosci. 16:149-64, 1998

Antoni FA: Vasopressinergic control of pituitary adrenocorticotropin secretion comes of age. Front Neuroendocrinol 14(2):76-122, 1993

Arana GW, Baldessarini RJ, Ornsteen M: The dexamethasone suppression test for diagnosis and prognosis in psychiatry. Commentary and review. Arch Gen Psychiatry 42(12):1193-204, 1985

Arato M, Banki CM, Nemeroff CB, Bissette G: Hypothalamic-pituitary-adrenal axis and suicide. Ann N Y Acad Sci. 487:263-70, 1986

Arato M, Banki CM, Bissette G, Nemeroff CB: Elevated CSF CRF in suicide victims. Biol Psychiatry. 25:355-9, 1989

Arborelius L, Owens MJ, Plotsky PM, Nemeroff CB: The role of corticotropin-releasing factor in depression and anxiety disorders. J Endocrinol. 160(1):1-12, 1999

Arnow BA: Relationships between childhood maltreatment, adult health and psychiatric outcomes, and medical utilization. J Clin Psychiatry 65 Suppl 12:10-5, 2004

Arnow BA, Hart S, Hayward C, Dea R, Barr Taylor C: Severity of child maltreatment, pain complaints and medical utilization among women. J Psychiatr Res 34(6):413-21, 2000

Asbach S, Schulz C, Lehnert H: Effects of corticotropin-releasing hormone on locus coeruleus neurons in vivo: a microdialysis study using a novel bilateral approach. Eur J Endocrinol 145(3):359-63, 2001

Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkinson CW. Stress hormone levels of children of depressed mothers. Dev Psychopathol 14(2):333-49, 2002

Astin MC, Lawrence KJ, Foy DW: Posttraumatic stress disorder among battered women: risk and resiliency factors. Violence Vict 8(1):17-28, 1993

Astin MC, Ogland-Hand SM, Coleman EM, Foy DS: Posttraumatic stress disorder and childhood abuse in battered women: comparisons with maritally distressed women. J Consult Clin Psychol 63(2):308-12, 1995

Atmaca M, Kuloglu M, Tezcan E, Onal S, Ustundag B: Neopterin levels and dexamethasone suppression test in posttraumatic stress disorder. Eur Arch Psychiatry Clin Neurosci 252(4):161-5, 2002

Austin MC, Janosky JE, Murphy HA: Increased corticotropin-releasing hormone immunoreactivity in monoamine-containing pontine nuclei of depressed suicide men. Mol Psychiatry 8(3):324-32, 2003

Baghai TC, Schule C, Zwanzger P, Minov C, Holme C, Padberg F, Bidlingmaier M, Strasburger CJ, Rupprecht R: Evaluation of a salivary based combined dexamethasone/CRH test in patients with major depression. Psychoneuroendocrinology. 27:385-99, 2002

Baker DG, West SA, Nicholson WE, Ekhator NN, Kasckow JW, Hill KK, Bruce AB, Orth DN, Geracioti TD Jr: Serial CSF corticotropin-releasing hormone levels and adrenocortical activity in combat veterans with posttraumatic stress disorder. Am J Psychiatry 156(4):585-8, 1999

Bale TL, Contarino A, Smith GW, Chan R, Gold LH, Sawchenko PE, Koob GF, Vale WW, Lee KF: Mice deficient for corticotropin-releasing hormone receptor-2 display anxiety-like behaviour and are hypersensitive to stress. Nat Genet 24(4):410-4, 2000

Bale TL, Vale WW: CRF and CRF receptors: role in stress responsivity and other behaviors. Annu Rev Pharmacol Toxicol 44:525-57, 2004

Balon R: Mood, anxiety, and physical illness: body and mind, or mind and body? Depress Anxiety 23(6):377-87, 2006

Banki CM, Karmacsi L, Bissette G, Nemeroff CB: CSF corticotropin-releasing hormone and somatostatin in major depression: response to antidepressant treatment and relapse. Eur Neuropsychopharmacol. 2:107-13, 1992

Bartanusz V, Aubry JM, Jezova D, Baffi J, Kiss JZ: Up-regulation of vasopressin mRNA in paraventricular hypophysiotrophic neurons after acute immobilization stress. Neuroendocrinology 58(6):625-9, 1993

Bartanusz V, Aubry JM, Steimer T, Baffi J, Kiss JZ: Stressor-specific increase of vasopressin mRNA in paraventricular hypophysiotrophic neurons. Neurosci Lett 170(1):35-8, 1994

Bartanusz V, Jezova D, Bertini LT, Tilders FJ, Aubry JM, Kiss JZ: Stress-induced increase in vasopressin and corticotropin-releasing factor expression in hypophysiotrophic paraventricular neurons. Endocrinology 132(2):895-902, 1993

Beatson J, Taryan S:Predisposition to depression: the role of attachment. Aust N Z J Psychiatry 37(2):219-25, 2003

Beck JC, van der Kolk B: Reports of childhood incest and current behavior of chronically hospitalized psychotic women. Am J Psychiatry 144(11):1474-6, 1987

Beitchman JH, Zucker KJ, Hood JE, daCosta GA, Akman D, Cassavia E: A review of the long-term effects of child sexual abuse. Child Abuse Negl 16(1):101-18, 1992

Belsky J: Theory testing, effect-size evaluation, and differential susceptibility to rearing influence: the case of mothering and attachment. Child Dev 68(4):598-600, 1997

Bertini LT, Kiss JZ: Hypophysiotrophic neurons are capable of altering the ratio of co-packaged neurohormones. Neuroscience 42(1):237-44, 1991

Bifulco A, Brown GW, Adler Z: Early sexual abuse and clinical depression in adult life. Br J Psychiatry 159:115-22, 1991

Bijl RV, Ravelli A, van Zessen G: Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS). Soc Psychiatry Psychiatr Epidemiol 33(12):587-95, 1998

Bisson J and Andrew M: Psychological treatment of post-traumatic stress disorder (PTSD). Cochrane Database Syst Rev CD003388, 2007

Blanchard EB, Buckley TC, Hickling EJ, Taylor AE: Posttraumatic stress disorder and comorbid major depression: is the correlation an illusion? J Anxiety Disord 12(1):21-37, 1998

Boscarino JA: Posttraumatic stress disorder, exposure to combat, and lower plasma cortisol among Vietnam veterans: findings and clinical implications. J Consult Clin Psychol 64(1):191-201, 1996

Boudewyn AC, Liem JH: Childhood sexual abuse as a precursor to depression and self-destructive behavior in adulthood. J Traumatic Stress 8:445-459, 1995

Braddock L: The dexamethasone suppression test. Fact and artefact. Br J Psychiatry. 148:363-74, 1986

Brady KT, Killeen TK, Brewerton T, Lucerini S: Comorbidity of psychiatric disorders and posttraumatic stress disorder. J Clin Psychiatry 61 Suppl 7:22-32, 2000

Brand B: Trauma and violence, in Women's Mental Health: A Comprehensive Textbook. Edited by Korstein SG and Clayton AH, New York, NY, The Guilford Press, 2004, pp 542-554

Brandenberger G, Charloux A, Gronfier C, Otzenberger H: Ultradian rhythms in hydromineral hormones. Horm Res 49(3-4):131-5, 1998

Bremner JD, Brett E: Trauma-related dissociative states and long-term psychopathology in posttraumatic stress disorder. J Trauma Stress 10(1):37-49, 1997

Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM: Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress 11(1):125-36, 1998

Bremner JD, Licinio J, Darnell A, Krystal JH, Owens MJ, Southwick SM, Nemeroff CB, Charney DS: Elevated CSF corticotropin-releasing factor concentrations in posttraumatic stress disorder. Am J Psychiatry 154(5):624-9, 1997

Bremner JD, Vythilingam M, Vermetten E, Adil J, Khan S, Nazeer A, Afzal N, McGlashan T, Elzinga B, Anderson GM, Heninger G, Southwick SM, Charney DS: Cortisol response to a cognitive stress challenge in posttraumatic stress disorder (PTSD) related to childhood abuse. Psychoneuroendocrinology 28(6):733-50, 2003

Breslau N: Epidemiologic studies of trauma, posttraumatic stress disorder, and other psychiatric disorders. Can J Psychiatry 47(10):923-9, 2002

Breslau N, Davis GC, Andreski P, Peterson E. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen Psychiatry 48(3):216-22, 1991

Breslau N, Kessler RC, Chilcoat HD, Schultz LR, Davis GC, Andreski P: Trauma and posttraumatic stress disorder in the community: the 1996 Detroit Area Survey of Trauma. Arch Gen Psychiatry 55(7):626-32, 1998

Breslau N, Schultz L, Peterson E: Sex differences in depression: a role for preexisting anxiety. Psychiatry Res 58(1):1-12, 1995

Brewin CR, Andrews B, Rose S, Kirk M: Acute stress disorder and posttraumatic stress disorder in victims of violent crime. Am J Psychiatry 156(3):360-6, 1999

Briere J: Child Abuse Trauma: Theory and Treatment of the Lasting Effects, Newbury Park, CA, Sage Publications, 1992

Briere J: Medical symptoms, health risk, and history of childhood sexual abuse. Mayo Clin Proc 67(6):603-4, 1992

Briere J and Elliot DM: Prevalence and psychological sequelae of self-reported childhood physical and sexual abuse in a general population sample of men and women. Child Abuse and Neglect 27:1205-1222, 2003

Briere J, Evans D, Runtz M, Wall T: Symptomatology in men who were molested as children: a comparison study. Am J Orthopsychiatry 58(3):457-61, 1988

Briere J, Gill E: Self-mutilation in clinical and general population samples: prevalence, correlates, and functions. Am J Orthopsychiatry 68(4):609-20, 1998

Briere J, Runtz M: Symptomatology associated with childhood sexual victimization in a nonclinical adult sample. Child Abuse Negl 12(1):51-9, 1988

Briere J, Zaidi LY: Sexual abuse histories and sequelae in female psychiatric emergency room patients. Am J Psychiatry 146(12):1602-6, 1989

Broadbear JH: Corticotropin-releasing hormone in nonhuman primates. Front Biosci 11:2303-35, 2006

Broadhead JC, Abas MA: Life events, difficulties and depression among women in an urban setting in Zimbabwe. Psychol Med 28(1):29-38, 1998

Bromet E, Sonnega A, Kessler RC: Risk factors for DSM-III-R posttraumatic stress disorder: findings from the National Comorbidity Survey. Am J Epidemiol 147(4):353-61, 1998

Brown ES, Varghese FP, McEwen BS: Association of depression with medical illness: does cortisol play a role? Biol Psychiatry 55(1):1-9, 2004

Brown DR, Milburn NG, Gary LE: Symptoms of depression among older African-Americans: an analysis of gender differences. Gerontologist 32(6):789-95, 1992

Brown GW, Harris TO, Hepworth C: Life events and endogenous depression. A puzzle reexamined. Arch Gen Psychiatry 51(7):525-34, 1994

Browne A, Finkelhor D: Impact of child sexual abuse: a review of the research. Psychol Bull 99(1):66-77, 1986

Bryant RA, Kemp AH, Felmingham KL, Liddell B, Olivieri G, Peduto A, Gordon E, Williams LM: Enhanced amygdala and medial prefrontal activation during nonconscious processing of fear in posttraumatic stress disorder: An fMRI study. Hum Brain Mapp 2007

Bryer JB, Nelson BA, Miller JB, Krol PA: Childhood sexual and physical abuse as factors in adult psychiatric illness. Am J Psychiatry 144(11):1426-30, 1987

Burke HM, Davis MC, Otte C, Mohr DC: Depression and cortisol responses to psychological stress: a meta-analysis. Psychoneuroendocrinology 30(9):846-56, 2005

Burnam MA, Stein JA, Golding JM, Siegel JM, Sorenson SB, Forsythe AB, Telles CA: Sexual assault and mental disorders in a community population. J Consult Clin Psychol. 56(6):843-50, 1988

Burrows HL, Nakajima M, Lesh JS, Goosens KA, Samuelson LC, Inui A, Camper SA, Seasholtz AF: Excess corticotropin releasing hormone-binding protein in the hypothalamic-pituitary-adrenal axis in transgenic mice. J Clin Invest 101(7):1439-47, 1998

Burt VK, Stein K: Epidemiology of depression throughout the female life cycle. J Clin Psychiatry 63 Suppl 7:9-15, 2002

Caldji C, Diorio J, Meaney MJ: Variations in maternal care alter GABA(A) receptor subunit expression in brain regions associated with fear. Neuropsychopharmacology 28(11):1950-9, 2003

Campbell JC: Health consequences of intimate partner violence. Lancet 359(9314):1331-6, 2002

Campbell JC, Soeken KL: Women's responses to battering: a test of the model. Res Nurs Health 22(1):49-58, 1999

Canteras NS, Simerly RB, Swanson LW: Organization of projections from the medial nucleus of the amygdala: a PHAL study in the rat. J Comp Neurol 360(2):213-45, 1995

Carrion VG, Weems CF, Ray RD, Glaser B, Hessl D, Reiss AL: Diurnal salivary cortisol in pediatric posttraumatic stress disorder. Biol Psychiatry 51(7):575-82, 2002

Carroll BJ, Feinberg M, Greden JF, Tarika J, Albala AA, Haskett RF, James NM, Kronfol Z, Lohr N, Steiner M, de Vigne JP, Young E: A specific laboratory test for the diagnosis of melancholia. Standardization, validation, and clinical utility. Arch Gen Psychiatry. 38:15-22, 1981

Carter JD, Joyce PR, Mulder RT, Luty SE, McKenzie J: Gender differences in the presentation of depressed outpatients: a comparison of descriptive variables. J Affect Disord 61(1-2):59-67, 2000

Cascio CS, Shinsako J, Dallman MF: The suprachiasmatic nuclei stimulate evening ACTH secretion in the rat. Brain Res 423(1-2):173-8, 1987

Cassano GB, Akiskal HS, Musetti L, Perugi G, Soriani A, Mignani V: Psychopathology, temperament, and past course in primary major depressions. 2. Toward a redefinition of bipolarity with a new semistructured interview for depression. Psychopathology 22(5):278-88, 1989

Cascardi M, Riggs DS, Hearstlkeda D, Foa EB: Objective ratings of assault safety as predictors of PTSD. J Interpersonal Violence 11(1): 65-78, 1996

Catalan R, Gallart JM, Castellanos JM, Galard R: Plasma corticotropin-releasing factor in depressive disorders. Biol Psychiatry. 44:15-20, 1998

Catlin DH, Gorelick DA, and Gerner RH: Clinical pharmacology of beta-endorphin in depression and schizophrenia. Ann N Y Acad Sci 398:434-447, 1982

Charney DS: Neuroanatomical circuits modulating fear and anxiety behaviors. Acta Psychiatr Scand Suppl (417):38-50, 2003

Charney DS: Psychobiological mechanisms of resilience and vulnerability: implications for successful adaptation to extreme stress. Am J Psychiatry 161(2):195-216, 2004

Choi WS, Patten CA, Gillin JC, Kaplan RM, Pierce JP: Cigarette smoking predicts development of depressive symptoms among U.S. adolescents. Ann Behav Med 19(1):42-50, 1997

Christensen MV, Kessing LV: The hypothalamo-pituitary-adrenal axis in major affective disorder: a review. Nord J Psychiatry. 55:359-63, 2001

Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis. JAMA. 267:1244-52, 1992

Chrousos GP and Kino T: Glucocorticoid action networks and complex psychiatric and/or somatic disorders. Stress 10(2):213-9, 2007

Chu JA, Frey LM, Ganzel BL, Matthews JA: Memories of childhood abuse: dissociation, amnesia, and corroboration. Am J Psychiatry 156(5):749-55, 1999

Cirulli F, Berry A, Alleva E: Early disruption of the mother-infant relationship: effects on brain plasticity and implications for psychopathology. Neurosci Biobehav Rev 27(1-2):73-82, 2003

Claes SJ: Corticotropin-releasing hormone (CRH) in psychiatry: from stress to psychopathology. Ann Med 36(1):50-61, 2004

Clark DB, Lesnick L, Hegedus AM: Traumas and other adverse life events in adolescents with alcohol abuse and dependence. J Am Acad Child Adolesc Psychiatry 36(12):1744-51, 1997

Classen CC, Palesh OG, Aggarwal R: Sexual revictimization: a review of the empirical literature. Trauma Violence Abuse 6(2):103-29, 2005

Cloutier S, Martin SL, Poole C: Sexual assault among North Carolina women: prevalence and health risk factors. J Epidemiol Community Health 56(4):265-71, 2002

Cohen H and Zohar J: An animal model of posttraumatic stress disorder: the use of cut-off behavioral criteria. Ann N Y Acad Sci 1032:167-78, 2004

Coker AL, Weston R, Creson DL, Justice B, Blakeney P: PTSD symptoms among men and women survivors of intimate partner violence: the role of risk and protective factors. Violence Vict 20(6):625-43, 2005

Cole MA, Kalman BA, Pace TW, Topczewski F, Lowrey MJ, Spencer RL: Selective blockade of the mineralocorticoid receptor impairs hypothalamic-pituitary-adrenal axis expression of habituation. J Neuroendocrinol 12(10):1034-42, 2000

Conger RD, Ge X, Elder GH Jr, Lorenz FO, Simons RL: Economic stress, coercive family process, and developmental problems of adolescents. Child Dev 65(2 Spec No):541-61, 1994

Cortright DN, Nicoletti A, Seasholtz AF: Molecular and biochemical characterization of the mouse brain corticotropin-releasing hormone-binding protein. Mol Cell Endocrinol 111(2):147-57, 1995

Costa A, Bono G, Martignoni E, Merlo P, Sances G, Nappi G: An assessment of hypothalamo-pituitary-adrenal axis functioning in non-depressed, early abstinent alcoholics. Psychoneuroendocrinology 21(3):263-75, 1996

Costa PT Jr, Terracciano A, McCrae RR: Gender differences in personality traits across cultures: robust and surprising findings. J Pers Soc Psychol 81(2):322-31, 2001

Coste SC, Kesterson RA, Heldwein KA, Stevens SL, Heard AD, Hollis JH, Murray SE, Hill JK, Pantely GA, Hohimer AR, Hatton DC, Phillips TJ, Finn DA, Low MJ,

Coupland NJ: Brain mechanisms and neurotransmitters in Post-Traumatic Stress Disorder: Diagnosis, Management and Treatment. Edited by Nutt D, Davidson JRT, Zohar J, London, UK: Martin Dunitz Ltd, 2000, pp 69-100

Coyne JC, Fechner-Bates S, Schwenk TL: Prevalence, nature, and comorbidity of depressive disorders in primary care. Gen Hosp Psychiatry 16(4):267-76, 1994

Crane JW, Buller KM, Day TA: Evidence that the bed nucleus of the stria terminalis contributes to the modulation of hypophysiotropic corticotropin-releasing factor cell responses to systemic interleukin-1beta. J Comp Neurol 467(2):232-42, 2003

Cromer KR, Sachs-Ericsson N: The association between childhood abuse, PTSD, and the occurrence of adult health problems: moderation via current life stress. J Trauma Stress 19(6):967-71, 2006

Cunningham ET Jr, Sawchenko PE: Anatomical specificity of noradrenergic inputs to the paraventricular and supraoptic nuclei of the rat hypothalamus. J Comp Neurol 274(1):60-76, 1988

Cutler SE, Nolen-Hoeksema S:Accounting for sex differences in depression through female victimization: Childhood sexual abuse. Sex Roles 24:425-438, 1991

Cyranowski JM, Frank E, Young E, Shear MK: Adolescent onset of the gender difference in lifetime rates of major depression: a theoretical model. Arch Gen Psychiatry 57(1):21-7, 2000

Dallman MF, Levin N, Cascio CS, Akana SF, Jacobson L, Kuhn RW: Pharmacological evidence that the inhibition of diurnal adrenocorticotropin secretion by corticosteroids is mediated via type I corticosterone-preferring receptors. Endocrinology 124(6):2844-50, 1989

Davidson J, Swartz M, Storck M, Krishnan RR, Hammett E: A diagnostic and family study of posttraumatic stress disorder. Am J Psychiatry 142(1):90-3, 1985

Davidson JR, Hughes D, Blazer DG, George LK: Post-traumatic stress disorder in the community: an epidemiological study. Psychol Med 21(3):713-21, 1991

Davidson JR, Kudler HS, Saunders WB, Smith RD: Symptom and comorbidity patterns in World War II and Vietnam veterans with posttraumatic stress disorder. Compr Psychiatry 31(2):162-70, 1990

Davis RC, Brickman E, Baker T: Supportive and unsupportive responses of others to rape victims: effects on concurrent victim adjustment. Am J Community Psychol 19(3):443-51, 1996

De Bellis MD, Chrousos GP, Dorn LD, Burke L, Helmers K, Kling MA, Trickett PK, Putnam FW: Hypothalamic-pituitary-adrenal axis dysregulation in sexually abused girls. J Clin Endocrinol Metab 78(2):249-55, 1994

De Bellis MD, Gold PW, Geracioti TD Jr, Listwak SJ, Kling MA: Association of fluoxetine treatment with reductions in CSF concentrations of corticotropin-releasing hormone and arginine vasopressin in patients with major depression. Am J Psychiatry. 150(4):656-7, 1993

De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND: A.E. Bennett Research Award. Developmental traumatology. Part II: Brain development. Biol Psychiatry 45(10):1271-84, 1999

de Goeij DC, Dijkstra H, Tilders FJ: Chronic psychosocial stress enhances vasopressin, but not corticotropin-releasing factor, in the external zone of the median eminence of male rats: relationship to subordinate status. Endocrinology 131(2):847-53, 1992

de Goeij DC, Kvetnansky R, Whitnall MH, Jezova D, Berkenbosch F, Tilders FJ: Repeated stress-induced activation of corticotropin-releasing factor neurons enhances vasopressin stores and colocalization with corticotropin-releasing factor in the median eminence of rats. Neuroendocrinology 53(2):150-9, 1991

de Goeij DC, Jezova D, Tilders FJ: Repeated stress enhances vasopressin synthesis in corticotropin releasing factor neurons in the paraventricular nucleus. Brain Res 577(1):165-8, 1992

de Kloet CS, Vermetten E, Geuze E, Kavelaars A, Heijnen CJ, Westenberg HG: Assessment of HPA-axis function in posttraumatic stress disorder: pharmacological and non-pharmacological challenge tests, a review. J Psychiatr Res 40(6):550-67, 2006

de Kloet ER, Vreugdenhil E, Oitzl MS, Joels M: Brain corticosteroid receptor balance in health and disease. Endocr Rev 19(3):269-301, 1998

de Wied D, Elands J, Kovacs G: Interactive effects of neurohypophyseal neuropeptides with receptor antagonists on passive avoidance behavior: mediation by a cerebral neurohypophyseal hormone receptor? Proc Natl Acad Sci U S A 88(4):1494-8, 1991

de Winter RF, van Hemert AM, DeRijk RH, Zwinderman KH, Frankhuijzen-Sierevogel AC, Wiegant VM, Goekoop JG: Anxious-retarded depression: relation with plasma vasopressin and cortisol. Neuropsychopharmacology 28(1):140-7, 2003

de Winter RF, Zwinderman KH, Goekoop JG: Anxious-retarded depression: relation to family history of depression. Psychiatry Res 127(1-2):111-9, 2004

Deering CG, Glover SG, Ready D, Eddleman HC, Alarcon RD: Unique patterns of comorbidity in posttraumatic stress disorder from different sources of trauma. Compr Psychiatry 37(5):336-46, 1996

Delahanty DL, Raimonde AJ, Spoonster E: Initial posttraumatic urinary cortisol levels predict subsequent PTSD symptoms in motor vehicle accident victims. Biol Psychiatry 48(9):940-7, 2000

Diagnostic and Statistical Manual of Mental Disorders: Washington, DC. American Psychiatric Association, Fourth Edition, Text Revision, 2000

Dickinson LM, deGruy FV 3rd, Dickinson WP, Candib LM: Complex posttraumatic stress disorder: evidence from the primary care setting. Gen Hosp Psychiatry 20(4):214-24, 1998

Dinan TG, Lavelle E, Scott LV, Newell-Price J, Medbak S, Grossman AB: Desmopressin normalizes the blunted adrenocorticotropin response to corticotropin-releasing hormone in melancholic depression: evidence of enhanced vasopressinergic responsivity. J Clin Endocrinol Metab 4(6):2238-40, 1999

Dolan RJ, Calloway SP, Fonagy P, De Souza FV, Wakeling A: Life events, depression and hypothalamic-pituitary-adrenal axis function. Br J Psychiatry 147:429-33, 1985

Dowson JH, Sussams P, Grounds AT, Taylor J: Associations of self-reported past "psychotic" phenomena with features of personality disorders. Compr Psychiatry 41(1):42-8, 2000

Du Vigneaud V: Hormones of the posterior pituitary gland: oxytocin and vasopressin. Harvey Lect 50:1-26, 1954-1955

Dube SR, Felitti VJ, Dong M, Giles WH, Anda RF: The impact of adverse childhood experiences on health problems: evidence from four birth cohorts dating back to 1900. Prev Med 37(3):268-77, 2003

Duncan RD, Saunders BE, Kilpatrick DG, Hanson RF, Resnick HS: Childhood physical assault as a risk factor for PTSD, depression, and substance abuse: findings from a national survey. Am J Orthopsychiatry 66(3):437-48, 1996

Dunn AJ, Berridge CW: Is corticotropin-releasing factor a mediator of stress responses? Ann N Y Acad Sci 579:183-91, 1990

Dunn AJ, Swiergiel AH: Behavioral responses to stress are intact in CRF-deficient mice. Brain Res 845(1):14-20, 1999

Dunn FL, Brennan TJ, Nelson AE, Robertson GL: The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 52(12):3212-9, 1973

Eby KK, Campbell JC, Sullivan CM, Davidson WS 2nd: Health effects of experiences of sexual violence for women with abusive partners. Health Care Women Int 16(6):563-76, 1995

Elliott DM, Mok DS, Briere J: Adult sexual assault: prevalence, symptomatology, and sex differences in the general population. J Trauma Stress 17(3):203-11, 2004

Elzinga BM, Schmahl CG, Vermetten E, van Dyck R, Bremner JD: Higher cortisol levels following exposure to traumatic reminders in abuse-related PTSD. Neuropsychopharmacology 28(9):1656-65, 2003

Engler D, Pham T, Fullerton MJ, Clarke IJ, Funder JW:Evidence for an ultradian secretion of adrenocorticotropin, beta-endorphin and alpha-melanocyte-stimulating hormone by the ovine anterior and intermediate pituitary. Neuroendocrinology 49(4):349-60, 1989

Epstein JN, Saunders BE, Kilpatrick DG: Predicting PTSD in women with a history of childhood rape. J Trauma Stress 10(4):573-88, 1997

Epstein RS, Fullerton CS, Ursano RJ: Posttraumatic stress disorder following an air disaster: a prospective study. Am J Psychiatry 155(7):934-8, 1998

Ericsson A, Arias C, Sawchenko PE: Evidence for an intramedullary prostaglandin-dependent mechanism in the activation of stress-related neuroendocrine circuitry by intravenous interleukin-1. J Neurosci 17(18):7166-79, 1997

Ericsson A, Kovacs KJ, Sawchenko PE: A functional anatomical analysis of central pathways subserving the effects of interleukin-1 on stress-related neuroendocrine neurons. J Neurosci 14(2):897-913, 1994

Fanous A, Gardner CO, Prescott CA, Cancro R, Kendler KS: Neuroticism, major depression and gender: a population-based twin study. Psychol Med 32(4):719-28, 2002

Farabaugh A, Mischoulon D, Fava M, Guyker W, Alpert J: The overlap between personality disorders and major depressive disorder (MDD). Ann Clin Psychiatry 16(4):217-24, 2004

Feinstein A, Dolan R: Predictors of post-traumatic stress disorder following physical trauma: an examination of the stressor criterion. Psychol Med 21(1):85-91, 1991

Felitti VJ: Long-term medical consequences of incest, rape, and molestation. South Med J 84(3):328-31, 1991

Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, Koss MP, Marks JS: Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults. The Adverse Childhood Experiences (ACE) Study. Am J Prev Med 14(4):245-58, 1998

Fenoglio KA, Brunson KL, Avishai-Eliner S, Chen Y, Baram TZ: Region-specific onset of handling-induced changes in corticotropin-releasing factor and glucocorticoid receptor expression. Endocrinology 145(6):2702-6, 2004

Ferrari E, Casarotti D, Muzzoni B, Albertelli N, Cravello L, Fioravanti M, Solerte SB, Magri F: Age-related changes of the adrenal secretory pattern: possible role in pathological brain aging. Brain Res Brain Res Rev 37(1-3):294-300, 2001

Fiddler M, Jackson J, Kapur N, Wells A, Creed F: Childhood adversity and frequent medical consultations. Gen Hosp Psychiatry 26(5):367-77, 2004

Finkelhor D, Hotaling G, Lewis IA, Smith C: Sexual abuse in a national survey of adult men and women: prevalence, characteristics, and risk factors. Child Abuse Negl 14(1):19-28, 1990

Fish EW, Shahrokh D, Bagot R, Caldji C, Bredy T, Szyf M, Meaney MJ: Epigenetic Programming of Stress Responses through Variations in Maternal Care. Ann N Y Acad Sci 1036:167-80, 2004

Foa EB, Riggs DS, Gershuny BS: Arousal, numbing, and intrusion: symptom structure of PTSD following assault. Am J Psychiatry 152(1):116-20, 1995

Ford JD, Kidd P: Early childhood trauma and disorders of extreme stress as predictors of treatment outcome with chronic posttraumatic stress disorder. J Trauma Stress 11(4):743-61, 1998

Foy DW, Sipprelle RC, Rueger DB, Carroll EM: Etiology of posttraumatic stress disorder in Vietnam veterans: analysis of premilitary, military, and combat exposure influences. J Consult Clin Psychol 52(1):79-87, 1984

Francis DD, Caldji C, Champagne F, Plotsky PM, Meaney MJ: The role of corticotropin-releasing factor--norepinephrine systems in mediating the effects of early experience on the development of behavioral and endocrine responses to stress. Biol Psychiatry 46(9):1153-66, 1999

Francis DD, Champagne FA, Liu D, Meaney MJ: Maternal care, gene expression, and the development of individual differences in stress reactivity. Ann N Y Acad Sci 896:66-84, 1999

Francis DD, Meaney MJ: Maternal care and the development of stress responses. Curr Opin Neurobiol 9(1):128-34, 1999

Frank E, Anderson B, Reynolds CF, III, Ritenour A, and Kupfer DJ: Life events and the research diagnostic criteria endogenous subtype. A confirmation of the distinction using the Bedford College methods. Arch Gen Psychiatry 51:519-524, 1994

Frank E, Carpenter LL, Kupfer DJ: Sex differences in recurrent depression: are there any that are significant? Am J Psychiatry 145(1):41-5, 1988

Friedman SB, Mason JW, Hamburg DA: Urinary 17-Hydroxycorticosteroid levels in parents of children with neoplastic disease. Psychosomatic Medicine 15(4):364–376, 1963

Gabilondo AM, Meana JJ, Garcia-Sevilla JA: Increased density of mu-opioid receptors in the postmortem brain of suicide victims. Brain Res 682(1-2):245-50, 1995

Galard R, Catalan R, Castellanos JM, and Gallart JM: Plasma corticotropin-releasing factor in depressed patients before and after the dexamethasone suppression test. Biol Psychiatry 51:463-468, 2002

Gelinas DJ: The persisting negative effects of incest. Psychiatry 46(4):312-32, 1983

Geracioti TD Jr, Loosen PT, Orth DN: Low cerebrospinal fluid corticotropin-releasing hormone concentrations in eucortisolemic depression. Biol Psychiatry 42:165-74, 1997

Geracioti TD Jr, Orth DN, Ekhator NN, Blumenkopf B, Loosen PT: Serial cerebrospinal fluid corticotropin-releasing hormone concentrations in healthy and depressed humans. J Clin Endocrinol Metab 74:1325-30, 1992

Gerstberger R, Fahrenholz F: Autoradiographic localization of V1 vasopressin binding sites in rat brain and kidney. Eur J Pharmacol 167(1):105-16, 1989

Gibbons JL: Cortisol secretion rate in depressive illness. Arch Gen Psychiatry 10:572-5, 1964

Gibbons JL, McHugh PR. Plasma cortisol in depressive illness. J Psychiatr Res 1:162-71, 1962

Gil-Rivas V, Fiorentine R, Anglin MD: Sexual abuse, physical abuse, and posttraumatic stress disorder among women participating in outpatient drug abuse treatment. J Psychoactive Drugs 28(1):95-102, 1996

Gillespie CF and Nemeroff CB: Hypercortisolemia and depression. Psychosom Med 67 Suppl 1:S26-8, 2005

Gillies GE, Linton EA, Lowry PJ: Corticotropin releasing activity of the new CRF is potentiated several times by vasopressin. Nature 299(5881):355-7, 1982

Gjerris A, Hammer M, Vendsborg P, Christensen NJ, Rafaelsen OJ: Cerebrospinal fluid vasopressin--changes in depression. Br J Psychiatry 147:696-701, 1985

Glod CA: Long-term consequences of childhood physical and sexual abuse. Arch Psychiatr Nurs 7(3):163-73, 1993

Goenjian AK, Yehuda R, Pynoos RS, Steinberg AM, Tashjian M, Yang RK, Najarian LM, Fairbanks LA: Basal cortisol, dexamethasone suppression of cortisol, and MHPG in adolescents after the 1988 earthquake in Armenia. Am J Psychiatry 153(7):929-34, 1996

Goekoop JG, de Winter RP, de Rijk R, Zwinderman KH, Frankhuijzen-Sierevogel A, Wiegant VM: Depression with above-normal plasma vasopressin: validation by relations with family history of depression and mixed anxiety and retardation. Psychiatry Res 141(2):201-11, 2006

Gold PW, Goodwin FK, Chrousos GP: Clinical and biochemical manifestations of depression. Relation to the neurobiology of stress. N Engl J Med 319(6):348-53, 1988

Golding JM: Sexual assault history and headache: five general population studies. J Nerv Ment Dis 187(10):624-9, 1999

Golding JM, Cooper ML, George LK: Sexual assault history and health perceptions: seven general population studies. Health Psychol 16(5):417-25, 1997

Golding JM, Wilsnack SC, Learman LA: Prevalence of sexual assault history among women with common gynecologic symptoms. Am J Obstet Gynecol 179(4):1013-9, 1998

Goodwin RD, Gotlib IH: Gender differences in depression: the role of personality factors. Psychiatry Res 126(2):135-42, 2004

Gormley GJ, Lowy MT, Reder AT, Hospelhorn VD, Antel JP, Meltzer HY: Glucocorticoid receptors in depression: relationship to the dexamethasone suppression test. Am J Psychiatry. 142:1278-84, 1985

Gotovac K, Sabioncello A, Rabatic S, Berki T, Dekaris D: Flow cytometric determination of glucocorticoid receptor (GCR) expression in lymphocyte subpopulations: lower quantity of GCR in patients with post-traumatic stress disorder (PTSD). Clin Exp Immunol 131(2):335-9, 2003

Green BL, Grace MC, Vary MG, Kramer TL, Gleser GC, Leonard AC: Children of disaster in the second decade: a 17-year follow-up of Buffalo Creek survivors. J Am Acad Child Adolesc Psychiatry 33(1):71-9, 1994

Greenwald E, Leitenberg H: Long-term effects of sexual experiences with siblings and nonsiblings during childhood. Arch Sex Behav 18(5):389-99, 1989

Griebel G, Simiand J, Serradeil-Le Gal C, Wagnon J, Pascal M, Scatton B, Maffrand JP, Soubrie P: Anxiolytic- and antidepressant-like effects of the non-peptide vasopressin V1b receptor antagonist, SSR149415, suggest an innovative approach for the treatment of stress-related disorders. Proc Natl Acad Sci U S A 99(9):6370-5, 2002

Griffin MG, Resick PA, Mechanic MB: Objective assessment of peritraumatic dissociation: psychophysiological indicators. Am J Psychiatry 154(8):1081-8, 1997

Halbreich U, Olympia J, Carson S, Glogowski J, Yeh CM, Axelrod S, Desu MM: Hypothalamo-pituitary-adrenal activity in endogenously depressed post-traumatic stress disorder patients. Psychoneuroendocrinology 14(5):365-70, 1989

Hall LA, Sachs B, Rayens MK, Lutenbacher M: Childhood physical and sexual abuse: their relationship with depressive symptoms in adulthood. Image J Nurs Sch 25(4):317-23, 1993

Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 23:56-62, 1960

Hankin BL, Abramson LY, Moffitt TE, Silva PA, McGee R, Angell KE: Development of depression from preadolescence to young adulthood: emerging gender differences in a 10-year longitudinal study. J Abnorm Psychol 107(1):128-40, 1998

Hashimoto K, Nishiyama M, Tanaka Y, Noguchi T, Asaba K, Hossein PN, Nishioka T, Makino S: Urocortins and corticotropin releasing factor type 2 receptors in the hypothalamus and the cardiovascular system. Peptides 25(10):1711-21, 2004

Hassan AH, Ableitner A, Stein C, Herz A: Inflammation of the rat paw enhances axonal transport of opioid receptors in the sciatic nerve and increases their density in the inflamed tissue. Neuroscience 55(1):185-95, 1993

Hauger RL, Lorang M, Irwin M, Aguilera G: CRF receptor regulation and sensitization of ACTH responses to acute ether stress during chronic intermittent immobilization stress. Brain Res 532(1-2):34-40, 1990

Hauger RL, Risbrough V, Brauns O, Dautzenberg FM: Corticotropin releasing factor (CRF) receptor signaling in the central nervous system: New molecular targets. CNS Neurol Disord Drug Targets 5:453-479, 2006

Hawk LW, Dougall AL, Ursano RJ, Baum A: Urinary catecholamines and cortisol in recent-onset posttraumatic stress disorder after motor vehicle accidents. Psychosom Med 62(3):423-34, 2000

Hegadoren KM, Lasiuk GC, Coupland NJ: Posttraumatic stress disorder Part III: health effects of interpersonal violence among women. Perspect Psychiatr Care 42(3):163-73, 2006

Heim C, Nemeroff CB: The impact of early adverse experiences on brain systems involved in the pathophysiology of anxiety and affective disorders. Biol Psychiatry 46(11):1509-22, 1999

Heim C, Newport DJ, Bonsall R, Miller AH, Nemeroff CB: Altered pituitary-adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. Am J Psychiatry 158(4):575-81, 2001

Heim C, Newport DJ, Heit S, Graham YP, Wilcox M, Bonsall R, Miller AH, Nemeroff CB: Pituitary-adrenal and autonomic responses to stress in women after sexual and physical abuse in childhood. JAMA 284(5):592-7, 2000

Heinrichs SC, Min H, Tamraz S, Carmouche M, Boehme SA, Vale WW: Anti-sexual and anxiogenic behavioral consequences of corticotropin-releasing factor overexpression are centrally mediated. Psychoneuroendocrinology 22(4):215-24, 1997

Helzer JE, Robins LN, McEvoy L: Post-traumatic stress disorder in the general population. Findings of the epidemiologic catchment area survey. N Engl J Med 317(26):1630-4, 1987

Henn FA, Vollmayr B: Stress models of depression: forming genetically vulnerable strains. Neurosci Biobehav Rev 29(4-5):799-804, 2005

Hennessy MB, Davis HN, McCrea AE, Harvey AT, Williams MT: Short- and long-term consequences of corticotropin-releasing factor in early development. Ann N Y Acad Sci 897:76-91, 1999

Herman J: Trauma and Recovery. New York, NY, Basic Books, 1997

Herman JP, Cullinan WE: Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends Neurosci 20(2):78-84, 1997

Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE: Central mechanisms of stress integration: hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. Front Neuroendocrinol 24(3):151-80, 2003

Herman JP, Ostrander MM, Mueller NK, Figueiredo H: Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Prog Neuropsychopharmacol Biol Psychiatry 29(8):1201-13, 2005

Herman JP, Prewitt CM, Cullinan WE: Neuronal circuit regulation of the hypothalamo-pituitary-adrenocortical stress axis. Crit Rev Neurobiol 10(3-4):371-94, 1996

Heuser I, Yassouridis A, Holsboer F: The combined dexamethasone/CRH test: a refined laboratory test for psychiatric disorders. J Psychiatr Res. 28:341-56, 1994

Hirschfeld RM, Klerman GL, Lavori P, Keller MB, Griffith P, Coryell W: Premorbid personality assessments of first onset of major depression. Arch Gen Psychiatry 46(4):345-50, 1989

Holmes MC, Antoni FA, Aguilera G, Catt KJ: Magnocellular axons in passage through the median eminence release vasopressin. Nature 319(6051):326-9, 1986

Holsboer F: CRHR1 antagonists as novel treatment strategies. CNS Spectr 6(7):590-4, 2001

Holsboer F: High-quality antidepressant discovery by understanding stress hormone physiology. Ann N Y Acad Sci 1007:394-404, 2003

Holsboer F, Barden N: Antidepressants and hypothalamic-pituitary-adrenocortical regulation. Endocr Rev. 17:187-205, 1996

Holsboer F, Lauer CJ, Schreiber W, Krieg JC: Altered hypothalamic-pituitary-adrenocortical regulation in healthy subjects at high familial risk for affective disorders. Neuroendocrinology. 62:340-7, 1995

Holsboer F, von Bardeleben U, Wiedemann K, Muller OA, Stalla GK: Serial assessment of corticotropin-releasing hormone response after dexamethasone in depression.

Implications for pathophysiology of DST nonsuppression. Biol Psychiatry. 22:228-34, 1987

Holsboer-Trachsler E, Stohler R, Hatzinger M: Repeated administration of the combined dexamethasone-human corticotropin releasing hormone stimulation test during treatment of depression. Psychiatry Res. 38:163-71, 1991

Horrocks PM, Jones AF, Ratcliffe WA, Holder G, White A, Holder R, Ratcliffe JG, London DR: Patterns of ACTH and cortisol pulsatility over twenty-four hours in normal males and females. Clin Endocrinol (Oxf) 32(1):127-34, 1990

Houskamp BM, Foy DW: The assessment of posttraumatic-stress-disorder in battered women. J Interpersonal Violence 6(3):367-375, 1991

Hunter R, Dick H, Christie JE, Goodwin GM, Fink G: Lymphocyte glucocorticoid receptor binding in depression: normal values following recovery. J Affect Disord. 14:155-9, 1988

Inder WJ, Donald RA, Prickett TC, Frampton CM, Sullivan PF, Mulder RT, Joyce PR: Arginine vasopressin is associated with hypercortisolemia and suicide attempts in depression. Biol Psychiatry 42(8):744-7, 1997

Inslicht SS, Marmar CR, Neylan TC, Metzler TJ, Hart SL, Otte C, McCaslin SE, Larkin GL, Hyman KB, Baum A: Increased cortisol in women with intimate partner violence-related posttraumatic stress disorder. Psychoneuroendocrinology 31(7):825-38, 2006

Iosifescu DV, Bankier B, Fava M: Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. Curr Psychiatry Rep 6(3):193-201, 2004

Janson W, Stein C: Peripheral opioid analgesia. Curr Pharm Biotechnol 4(4):270-4, 2003

Jard S, Guillon G, Balestre MN, Kirk C: WRK1 cells: a model system for studying properties of V1a vasopressin receptors. J Cardiovasc Pharmacol 8 Suppl 7:S12-7, 1986

Jedema HP, Grace AA: Corticotropin-releasing hormone directly activates noradrenergic neurons of the locus ceruleus recorded in vitro. J Neurosci 24(43):9703-13, 2004

Jeong KH, Jacobson L, Pacák K, Widmaier EP, Goldstein DS, Majzoub JA: Impaired basal and restraint-induced epinephrine secretion in corticotropin-releasing hormone-deficient mice. Endocrinology 141(3):1142-50, 2000

Jia LG, Canny BJ, Orth DN, Leong DA: Distinct classes of corticotropes mediate corticotropin-releasing hormone- and arginine vasopressin-stimulated adrenocorticotropin release. Endocrinology 128(1):197-203, 1991

Johnson DM, Pike JL, Chard KM. Factors predicting PTSD, depression, and dissociative severity in female treatment-seeking childhood sexual abuse survivors. Child Abuse Negl 25(1):179-98, 2001

Kalantaridou S, Makrigiannakis A, Zoumakis E, Chrousos GP: Peripheral corticotropin-releasing hormone is produced in the immune and reproductive systems: actions, potential roles and clinical implications. Front Biosci 12:572-80, 2007

Kaplan MJ and Klinetob NA: Childhood emotional trauma and chronic posttraumatic stress disorder in adult outpatients with treatment-resistanct depression. J Nerv Ment Dis 188:596-601, 2000

Kanter ED, Wilkinson CW, Radant AD, Petrie EC, Dobie DJ, McFall ME, Peskind ER, Raskind MA: Glucocorticoid feedback sensitivity and adrenocortical responsiveness in posttraumatic stress disorder. Biol Psychiatry 50(4):238-45, 2001

Karl A, Schaefer M, Malta LS, Dorfel D, Rohleder N, Werner A: A meta-analysis of structural brain abnormalities in PTSD. Neurosci Biobehav Rev 30(7):1004-31, 2006

Kasckow JW, Baker D, Geracioti TD Jr: Corticotropin-releasing hormone in depression and post-traumatic stress disorder. Peptides 22(5):845-51, 2001

Kathol RG, Jaeckle RS, Lopez JF, Meller WH: Consistent reduction of ACTH responses to stimulation with CRH, vasopressin and hypoglycaemia in patients with major depression. Br J Psychiatry 155:468-78, 1989

Kaufman J, Birmaher B, Perel J, Dahl RE, Moreci P, Nelson B, Wells W, Ryan ND: The corticotropin-releasing hormone challenge in depressed abused, depressed nonabused, and normal control children. Biol Psychiatry 42(8):669-79, 1997

Keller U: From obesity to diabetes. Int J Vitam Nutr Res 76(4):172-7, 2006

Keller-Wood ME, Dallman MF: Corticosteroid inhibition of ACTH secretion. Endocr Rev 5(1):1-24, 1984

Kellner M, Yassouridis A, Hubner R, Baker DG, Wiedemann K: Endocrine and cardiovascular responses to corticotropin-releasing hormone in patients with posttraumatic stress disorder: a role for atrial natriuretic peptide? Neuropsychobiology 47(2):102-8, 2003

Kendall-Tackett K: The health effects of childhood abuse: four pathways by which abuse can influence health. Child Abuse Negl 26(6-7):715-29, 2002

Kendler KS, Kessler RC, Neale MC, Heath AC, Eaves LJ: The prediction of major depression in women: toward an integrated etiologic model. Am J Psychiatry 150(8):1139-48, 1993

Kendler KS, Gardner CO, Prescott CA: Toward a comprehensive developmental model for major depression in women. Am J Psychiatry 159(7):1133-45, 2002

Kendler KS, Kuhn J, Prescott CA: The interrelationship of neuroticism, sex, and stressful life events in the prediction of episodes of major depression. Am J Psychiatry 161(4):631-6, 2004

Kendler KS, Thornton LM, Gardner CO: Stressful life events and previous episodes in the etiology of major depression in women: an evaluation of the "kindling" hypothesis. Am J Psychiatry 157(8):1243-51, 2000

Kendler KS, Thornton LM, Gardner CO: Genetic risk, number of previous depressive episodes, and stressful life events in predicting onset of major depression. Am J Psychiatry 158(4):582-6, 2001

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen HU, Kendler KS: Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. Arch Gen Psychiatry 51(1):8-19, 1994

Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB: Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 52(12):1048-60, 1995

Kessler RC, Turner JB, House JS: Intervening processes in the relationship between unemployment and health. Psychol 17(4):949-61, 1987

Kilpatrick DG, Best CL, Saunders BE, Veronen LJ. Rape in marriage and in dating relationships: how bad is it for mental health? Ann N Y Acad Sci 528:335-44, 1988

Kim J, Gorman J: The psychobiology of anxiety. Clin Neurosci Res 4:335-347, 2005

Kimerling R, Clum GA, Wolfe J: Relationships among trauma exposure, chronic posttraumatic stress disorder symptoms, and self-reported health in women: replication and extension. J Trauma Stress 13(1):115-28, 2000

Kirby LG, Rice KC, Valentino RJ. Effects of corticotropin-releasing factor on neuronal activity in the serotonergic dorsal raphe nucleus. Neuropsychopharmacology 22(2):148-62, 2000

Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH: Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosom Med 61(2):154-62, 1999

Kling MA, Roy A, Doran AR, Calabrese JR, Rubinow DR, Whitfield HJ Jr, May C, Post RM, Chrousos GP, Gold PW: Cerebrospinal fluid immunoreactive corticotropin-releasing

hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. J Clin Endocrinol Metab. 72:260-71, 1991

Knepel W, Przewlocki R, Nutto D, Herz A: Foot shock stress-induced release of vasopressin in adenohypophysectomized and hypophysectomized rats. Endocrinology 117(1):292-9, 1985

Kolb LC: Heterogeneity of PTSD. Am J Psychiatry 146(6):811-2, 1989

Koob GF: Corticotropin-releasing factor, norepinephrine, and stress. Biol Psychiatry 46(9):1167-80, 1999

Koob GF, Heinrichs SC, Pich EM, Menzaghi F, Baldwin H, Miczek K, Britton KT: The role of corticotropin-releasing factor in behavioural responses to stress. Ciba Found Symp 172:277-89, 1993

Koopman C, Classen C, Spiegel D: Predictors of posttraumatic stress symptoms among survivors of the Oakland/Berkeley, Calif., firestorm. Am J Psychiatry 151(6):888-94, 1994

Kornstein SG, Schatzberg AF, Thase ME, Yonkers KA, McCullough JP, Keitner GI, Gelenberg AJ, Ryan CE, Hess AL, Harrison W, Davis SM, Keller MB: Gender differences in chronic major and double depression. J Affect Disord 60(1):1-11, 2000

Koss MP, Koss PG, Woodruff WJ: Deleterious effects of criminal victimization on women's health and medical utilization. Arch Intern Med 151(2):342-7, 1991

Kosten TR, Wahby V, Giller E Jr, Mason J: The dexamethasone suppression test and thyrotropin-releasing hormone stimulation test in posttraumatic stress disorder. Biol Psychiatry 28(8):657-64, 1990

Kraus RP, Grof P, Brown GM: Drugs and the DST: need for a reappraisal. Am J Psychiatry 145(6):666-74, 1988

Kudler H, Davidson J, Meador K, Lipper S, Ely T: The DST and posttraumatic stress disorder. Am J Psychiatry 144(8):1068-71, 1987

Kuhn CM, Pauk J, Schanberg SM: Endocrine responses to mother-infant separation in developing rats. Dev Psychobiol 23(5):395-410, 1990

Künzel HE, Zobel AW, Nickel T, Ackl N, Uhr M, Sonntag A, Ising M, Holsboer F: Treatment of depression with the CRH-1-receptor antagonist R121919: endocrine changes and side effects. J Psychiatr Res 37(6):525-33, 2003

Ladd CO, Owens MJ, Nemeroff CB: Persistent changes in corticotropin-releasing factor neuronal systems induced by maternal deprivation. Endocrinology. 137:1212-8, 1996

Lamberts SW, Verleun T, Oosterom R, de Jong F, Hackeng WH: Corticotropin-releasing factor (ovine) and vasopressin exert a synergistic effect on adrenocorticotropin release in man. J Clin Endocrinol Metab 58(2):298-303, 1984

Langbehn DR, Pfohl B: Clinical correlates of self-mutilation among psychiatric inpatients. Ann Clin Psychiatry 5(1):45-51, 1993

Lavori PW, Dawson R, Mueller TB: Causal estimation of time-varying treatment effects in observational studies: application to depressive disorder. Stat Med 13(11):1089-100., 1994

Lavie P, Luboshitzky R, Kleinhouse N, Shen-Orr Z, Barzilai D, Glick SM, Leroith D, Levy J: Rhythms in urine flow are not correlated with rhythmic secretion of antidiuretic hormone (ADH) in well hydrated men. Horm Metab Res 12(2):66-70, 1980

László FA, Laczi F, Janáky T, Baláspiri L: Effect of vasopressin antagonist d(CH2)5Tyr(Et)VAVP on plasma arginine vasopressin level after osmotic stimulus. Endocr Regul 25(3):181-3, 1991

Lechner ME, Vogel ME, Garcia-Shelton LM, Leichter JL, Steibel KR: Self-reported medical problems of adult female survivors of childhood sexual abuse. J Fam Pract 36(6):633-8, 1993

Lee R: Childhood trauma and personality disorder: toward a biological model. Curr Psychiatry Rep 8(1):43-52, 2006

Leibenluft E, Clark CH, Myers FS: The reproducibility of depressive and hypomanic symptoms across repeated episodes in patients with rapid-cycling bipolar disorder. J Affect Disord 33(2):83-8, 1995

Lemieux AM, Coe CL: Abuse-related posttraumatic stress disorder: evidence for chronic neuroendocrine activation in women. Psychosom Med 57(2):105-15, 1995

Levinson DF: The genetics of depression: a review. Biol Psychiatry 60(2):84-92, 2006

Liberzon I, Phan KL: Brain-imaging studies of posttraumatic stress disorder. CNS Spectr 8(9):641-50, 2003

Lindberg FH, Distad LJ: Post-traumatic stress disorders in women who experienced childhood incest. Child Abuse Negl 9(3):329-34, 1985

Lindley SE, Carlson EB, Benoit M: Basal and dexamethasone suppressed salivary cortisol concentrations in a community sample of patents with posttraumatic stress disorder. Biol Psychiatry 55(9):940-5, 2004

Liu D, Caldji C, Sharma S, Plotsky PM, Meaney MJ: Influence of neonatal rearing conditions on stress-induced adrenocorticotropin responses and norepinepherine release in the hypothalamic paraventricular nucleus. J Neuroendocrinol 12(1):5-12, 2000

Lolait SJ, O'Carroll AM, Brownstein MJ: Molecular biology of vasopressin receptors. Ann N Y Acad Sci 771:273-92, 1995

Lolait SJ, Stewart LQ, Jessop DS, Young WS 3rd, O'Carroll AM: The hypothalamic-pituitary-adrenal axis response to stress in mice lacking functional vasopressin V1b receptors. Endocrinology 148(2):849-56, 2007

Lopez JF, Chalmers DT, Little KY, Watson SJ: A.E. Bennett Research Award. Regulation of serotonin1A, glucocorticoid, and mineralocorticoid receptor in rat and human hippocampus: implications for the neurobiology of depression. Biol Psychiatry 43(8):547-73, 1998

Lovejoy DA, Aubry JM, Turnbull A, Sutton S, Potter E, Yehling J, Rivier C, Vale WW: Ectopic expression of the CRF-binding protein: minor impact on HPA axis regulation but induction of sexually dimorphic weight gain. J Neuroendocrinol 10(7):483-91, 1998

Lovenberg TW, Chalmers DT, Liu C, De Souza EB: CRF2 alpha and CRF2 beta receptor mRNAs are differentially distributed between the rat central nervous system and peripheral tissues. Endocrinology 136(9):4139-42, 1995

Lowry PJ, Woods RJ, Baigent S: Corticotropin releasing factor and its binding protein. Pharmacol Biochem Behav 54(1):305-8, 1996

Lutz-Bucher B, Koch B: Influence of posterior pituitary hormones on the pituitary-adrenocortical response to neurogenic stress in the Brattleboro rat. Ann N Y Acad Sci 394:634-8, 1982

Maccari S, Darnaudery M, Morley-Fletcher S, Zuena AR, Cinque C, Van Reeth O: Prenatal stress and long-term consequences: implications of glucocorticoid hormones. Neurosci Biobehav Rev 27(1-2):119-27, 2003

MacMillan HL, Fleming JE, Trocme N, Boyle MH, Wong M, Racine YA, Beardslee WR, Offord DR: Prevalence of child physical and sexual abuse in the community. Results from the Ontario Health Supplement. JAMA 278(2):131-5, 1997

Maes M, Lin A, Bonaccorso S, van Hunsel F, Van Gastel A, Delmeire L, Biondi M, Bosmans E, Kenis G, Scharpe S; Increased 24-hour urinary cortisol excretion in patients with post-traumatic stress disorder and patients with major depression, but not in patients with fibromyalgia. Acta Psychiatr Scand 98(4):328-35, 1998

Maguire TM, Thakore J, Dinan TG, Hopwood S, Breen KC: Plasma sialyltransferase levels in psychiatric disorders as a possible indicator of HPA axis function. Biol Psychiatry. 41:1131-6, 1997

Maillet A, Gunga HC, Gauquelin G, Fortrat JO, Hope A, Rocker L, Kirsch K, Gharib C: Effects of 28-day isolation (ESA-ISEMSI'90) on blood pressure and blood volume regulating hormones. Aviat Space Environ Med 64(4):287-94, 1993

Makino S, Shibasaki T, Yamauchi N, Nishioka T, Mimoto T, Wakabayashi I, Gold PW, Hashimoto K: Psychological stress increased corticotropin-releasing hormone mRNA and content in the central nucleus of the amygdala but not in the hypothalamic paraventricular nucleus in the rat. Brain Res 850(1-2):136-43, 1999

Malerbi DA, Fragoso MC, Vieira Filho AH, Brenlha EM, Mendonça BB: Cortisol and adrenocorticotropin response to desmopressin in women with Cushing's disease compared with depressive illness. J Clin Endocrinol Metab 81(6):2233-7, 1996

Mancini C, Van Ameringen M, MacMillan H: Relationship of childhood sexual and physical abuse to anxiety disorders. J Nerv Ment Dis 183(5): 309-14, 1995

Marmar CR, Weiss DS, Schlenger WE, Fairbank JA, Jordan BK, Kulka RA, Hough RL.: Peritraumatic dissociation and posttraumatic stress in male Vietnam theater veterans. Am J Psychiatry 151(6):902-7, 1994

Martsolf DS and Draucker CB: Psychotherapy approaches for adult survivors of childhood sexual abuse: an integrative review of outcomes research. Issues Ment Heath Nurs 26(8):801-25, 2005

Mason JW, Giller EL, Kosten TR, Ostroff RB, Podd L: Urinary free-cortisol levels in posttraumatic stress disorder patients. J Nerv Ment Dis 174(3):145-9, 1986

Mastorakos G, Karoutsou EI, Mizamtsidi M: Corticotropin releasing hormone and the immune/inflammatory response. Eur J Endocrinol 155 Suppl 1:S77-84, 2006

Mayou R, Bryant B, Duthie R: Psychiatric consequences of road traffic accidents. BMJ 307(6905):647-51, 1993

McEwen BS: Mood disorders and allostatic load. Biol Psychiatry 54(3):200-7, 2003

McEwen BS: Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 1032:1-7, 2004

McEwen BS: Stress and hippocampal plasticity. Annu Rev Neurosci 22:105-22, 1999

McEwen BS: The neurobiology and neuroendocrinology of stress. Implications for post-traumatic stress disorder from a basic science perspective. Psychiatr Clin North Am 25(2):469-94, ix, 2002

McEwen BS: The neurobiology of stress: from serendipity to clinical relevance. Brain Res 886(1-2):172-189, 2000

McEwen BS, Stellar E: Stress and the individual. Mechanisms leading to disease. Arch Intern Med 153(18):2093-101, 1993

McFarlane AC: The effects of stressful life events and disasters: research and theoretical issues. Aust N Z J Psychiatry 19(4):409-21, 1985

McFarlane AC: Recent life events and psychiatric disorder in children: the interaction with preceding extreme adversity. J Child Psychol Psychiatry 29(5):677-90, 1988

McFarlane AC: The treatment of post-traumatic stress disorder. Br J Med Psychol 62 (Pt 1):81-90, 1989

McFarlane AC, Atchison M, Rafalowicz E, Papay P: Physical symptoms in post-traumatic stress disorder. J Psychosom Res 38(7):715-26, 1994

McHugo GJ, Caspi Y, Kammerer N, Mazelis R, Jackson EW, Russell L, Clark C, Liebschutz J, Kimerling R: The assessment of trauma history in women with co-occurring substance abuse and mental disorders and a history of interpersonal violence. J Behav Health Serv Res 32(2):113-27, 2005

McKay LI, Cidlowski JA: Cross-talk between nuclear factor-kappa B and the steroid hormone receptors: mechanisms of mutual antagonism. Mol Endocrinol 12(1):45-56, 1998

McKinney WT: Animal models of depression: an overview. Psychiatr Dev. 2:77-96, 1984

McNutt LA, Carlson BE, Persaud M, Postmus J: Cumulative abuse experiences, physical health and health behaviors. Ann Epidemiol 12(2):123-30, 2002

Meador-Woodruff JH, Greden JF: Effects of psychotropic medications on hypothalamic-pituitary-adrenal regulation. Endocrinol Metab Clin North Am 17(1):225-34, 1988

Meaney MJ, Aitken DH, Viau V, Sharma S, Sarrieau A: Neonatal handling alters adrenocortical negative feedback sensitivity and hippocampal type II glucocorticoid receptor binding in the rat. Neuroendocrinology 50(5):597-604, 1989

Meaney MJ, Diorio J, Francis D, Widdowson J, LaPlante P, Caldji C, Sharma S, Seckl JR, Plotsky PM: Early environmental regulation of forebrain glucocorticoid receptor gene expression: implications for adrenocortical responses to stress. Dev Neurosci 18(1-2):49-72, 1996

Meaney MJ, Viau V, Aitken DH, Bhatnagar S: Stress-induced occupancy and translocation of hippocampal glucocorticoid receptors. Brain Res 445(1):198-203, 1988

Meller I, Fichter MM, Schroppel H: Incidence of depression in octo- and nonagenerians: results of an epidemiological follow-up community study. Eur Arch Psychiatry Clin Neurosci 246(2):93-9, 1996

Meller WH, Kathol RC, Jaeckle RS, Lopez JF: Stimulation of the pituitary-adrenal axis with arginine vasopressin in patients with depression. J Psychiatr Res 21(3):269-77, 1987

Menzaghi F, Heinrichs SC, Pich EM, Weiss F, Koob GF: The role of limbic and hypothalamic corticotropin-releasing factor in behavioral responses to stress. Ann N Y Acad Sci. 697:142-54, 1993

Merali Z, Khan S, Michaud DS, Shippy SA, Anisman H: Does amygdaloid corticotropin-releasing hormone (CRH) mediate anxiety-like behaviors? Dissociation of anxiogenic effects and CRH release. Eur J Neurosci 20(1):229-39, 2004

Merali Z, Michaud D, McIntosh J, Kent P, Anisman H: Differential involvement of amygdaloid CRH system(s) in the salience and valence of the stimuli. Prog Neuropsychopharmacol Biol Psychiatry 27(8):1201-12, 2003

Mertin P, Mohr PB: A follow-up study of posttraumatic stress disorder, anxiety, and depression in Australian victims of domestic violence. Violence Vict 16(6):645-54, 2001

Meyerhoff JL, Oleshansky MA, Kalogeras KT, Mougey EH, Chrousos GP, Granger LG: Neuroendocrine responses to emotional stress: possible interactions between circulating factors and anterior pituitary hormone release. Adv Exp Med Biol 274:91-111, 1990

Modell S, Lauer CJ, Schreiber W, Huber J, Krieg JC, Holsboer F: Hormonal response pattern in the combined DEX-CRH test is stable over time in subjects at high familial risk for affective disorders. Neuropsychopharmacology. 18:253-62, 1998

Molchan SE, Hill JL, Martinez RA, Lawlor BA, Mellow AM, Rubinow DR, Bissette G, Nemeroff CB, Sunderland T: CSF somatostatin in Alzheimer's disease and major depression: relationship to hypothalamic-pituitary-adrenal axis and clinical measures. Psychoneuroendocrinology. 18:509-19, 1993

Moriceau S, Sullivan RM: Neurobiology of infant attachment. Dev Psychobiol 47(3):230-42, 2005

Morton N, Browne KD: Theory and observation of attachment and its relation to child maltreatment: a review. Child Abuse Negl 22(11):1093-104, 1998

Mouri T, Itoi K, Takahashi K, Suda T, Murakami O, Yoshinaga K, Andoh N, Ohtani H, Masuda T, Sasano N: Colocalization of corticotropin-releasing factor and vasopressin in the paraventricular nucleus of the human hypothalamus. Neuroendocrinology 57(1):34-9, 1993

Mueser KT, Salyers MP, Rosenberg SD, Goodman LA, Essock SM, Osher FC, Swartz MS, Butterfield MI; 5 Site Health and Risk Study Research Committee: Interpersonal trauma and posttraumatic stress disorder in patients with severe mental illness: demographic, clinical, and health correlates. Schizophr Bull 30(1):45-57, 2004

Muglia L, Jacobson L, Dikkes P, Majzoub JA: Corticotropin-releasing hormone deficiency reveals major fetal but not adult glucocorticoid need. Nature 373(6513):427-32, 1995

Müller MB, Landgraf R, Preil J, Sillaber I, Kresse AE, Keck ME, Zimmermann S, Holsboer F, Wurst W: Selective activation of the hypothalamic vasopressinergic system in mice deficient for the corticotropin-releasing hormone receptor 1 is dependent on glucocorticoids. Endocrinology 141(11):4262-9, 2000

Mulvihill D: The health impact of childhood trauma: an interdisciplinary review, 1997-2003. Issues Compr Pediatr Nurs 28(2):115-36, 2005

Murakami K, Hashimoto K, Ota Z: Interaction of synthetic ovine corticotropin releasing factor and arginine vasopressin on in vitro ACTH release by the anterior pituitary of rats. Neuroendocrinology 39(1):49-53, 1984

Murray CJ, Lopez AD: Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 349:1436-42, 1997

Najavits LM, Gastfriend DR, Barber JP, Reif S, Muenz LR, Blaine J, Frank A, Crits-Christoph P, Thase M, Weiss RD: Cocaine dependence with and without PTSD among subjects in the National Institute on Drug Abuse Collaborative Cocaine Treatment Study. Am J Psychiatry 155(2):214-9, 1998

Najavits LM, Weiss RD, Shaw SR: The link between substance abuse and posttraumatic stress disorder in women. A research review. Am J Addict 6(4):273-83, 1997

Negro-Vilar A, Saavedra JM: Changes in brain somatostatin and vasopressin levels after stress in spontaneously hypertensive and Wistar-Kyoto rats. Brain Res Bull 5(4):353-8, 1980

Nakase S, Kitayama I, Soya H, Hamanaka K, Nomura J: Increased expression of magnocellular arginine vasopressin mRNA in paraventricular nucleus of stress-induced depression-model rats. Life Sci 63(1):23-31, 1998

Nelson JC, Davis JM: DST studies in psychotic depression: a meta-analysis. Am J Psychiatry 154(11):1497-503, 1997

Nemeroff CB: Augmentation strategies in patients with refractory depression. Depress Anxiety. 4:169-81, 1996-1997

Nemeroff CB: The corticotropin-releasing factor (CRF) hypothesis of depression: new findings and new directions. Mol Psychiatry 1:336-342, 1996

Nemeroff CB: The neurobiology of depression. Sci Am. 278:42-9, 1998

Nemeroff CB, Bissette G, Akil H, Fink M: Neuropeptide concentrations in the cerebrospinal fluid of depressed patients treated with electroconvulsive therapy. Corticotrophin-releasing factor, beta-endorphin and somatostatin. Br J Psychiatry. 158:59-63, 1991

Nemeroff CB, Widerlov E, Bissette G, Walleus H, Karlsson I, Eklund K, Kilts CD, Loosen PT, Vale W: Elevated concentrations of CSF corticotropin-releasing factor-like immunoreactivity in depressed patients. Science 226:1342-4, 1984

Nemeroff CB, Vale WW: The neurobiology of depression: inroads to treatment and new drug discovery. J Clin Psychiatry 66 Suppl 7:5-13, 2005

Newman MG, Clayton L, Zuellig A, Cashman L, Arnow B, Dea R, Taylor CB: The relationship of childhood sexual abuse and depression with somatic symptoms and medical utilization. Psychol Med 30(5):1063-77, 2000

Newport DJ, Heim C, Bonsall R, Miller AH, Nemeroff CB: Pituitary-adrenal responses to standard and low-dose dexamethasone suppression tests in adult survivors of child abuse. Biol Psychiatry 55(1):10-20, 2004

Nolen-Hoeksema S: Responses to depression and their effects on the duration of depressive episodes. J Abnorm Psychol 100(4):569-82, 1991

Nolen-Hoeksema S: The role of rumination in depressive disorders and mixed anxiety/depressive symptoms. J Abnorm Psychol 109(3):504-11, 2000

Nolen-Hoeksema S, Larson J, Grayson C: Explaining the gender difference in depressive symptoms. J Pers Soc Psychol 77(5):1061-72, 1999

Nolen-Hoeksema S, McBride A, Larson J: Rumination and psychological distress among bereaved partners. J Pers Soc Psychol 72(4):855-62, 1997

Nolen-Hoeksema S, Parker LE, Larson J: Ruminative coping with depressed mood following loss. J Pers Soc Psychol 67(1):92-104, 1994

Noll JG: Does childhood sexual abuse set in motion a cycle of violence against women?: what we know and what we need to learn. J Interpers Violence 20(4):455-62, 2005

Norris FH, Kaniasty K: Psychological distress following criminal victimization in the general population: cross-sectional, longitudinal, and prospective analyses. J Consult Clin Psychol 62(1):111-23, 1994

O'Donnell D, Larocque S, Seckl JR, Meaney MJ: Postnatal handling alters glucocorticoid, but not mineralocorticoid messenger RNA expression in the hippocampus of adult rats. Brain Res Mol Brain Res 26(1-2):242-8, 1994

O'Donnell T, Hegadoren KM, Coupland NC: Noradrenergic mechanisms in the pathophysiology of post-traumatic stress disorder. Neuropsychobiology 50(4):273-83, 2004

Owens MJ, Nemeroff CB: Physiology and pharmacology of corticotropin-releasing factor. Pharmacol Rev 43(4):425-73, 1991

Palkovits M: Interconnections between the neuroendocrine hypothalamus and the central autonomic system. Geoffrey Harris Memorial Lecture, Kitakyushu, Japan, October 1998. Front Neuroendocrinol 20(4):270-95, 1999

Pariante CM: The glucocorticoid receptor: part of the solution or part of the problem? J Psychopharmacol 20(4 Suppl):79-84, 2006

Pariante CM, Miller AH: Glucocorticoid receptors in major depression: relevance to pathophysiology and treatment. Biol Psychiatry. 49:391-404, 2001

Parry BL: Reproductive factors affecting the course of affective illness in women. Psychiatr Clin North Am 12(1):207-20, 1989

Pasquali R, Vicennati V, Cacciari M, Pagotto U: The hypothalamic-pituitary-adrenal axis activity in obesity and the metabolic syndrome. Ann N Y Acad Sci 1083:111-28, 2006

Pearce D, Yamamoto KR: Mineralocorticoid and glucocorticoid receptor activities distinguished by nonreceptor factors at a composite response element. Science 259(5098):1161-5, 1993

Peeters F, Nicolson NA, Berkhof J: Levels and variability of daily life cortisol secretion in major depression. Psychiatry Res 126(1):1-13, 2004

Pelcovitz D, van der Kolk B, Roth S, Mandel F, Kaplan S, Resick P: Development of a criteria set and a structured interview for disorders of extreme stress (SIDES). J Trauma Stress 10(1):3-16, 1997

Perrin M, Donaldson C, Chen R, Blount A, Berggren T, Bilezikjian L, Sawchenko P, Vale W: Identification of a second corticotropin-releasing factor receptor gene and characterization of a cDNA expressed in heart. Proc Natl Acad Sci U S A 92(7):2969-73, 1995

Perris H: Life events and depression. Part 3. Relation to severity of the depressive syndrome. J Affect Disord 7(1):37-44, 1984

Pettigrew J, Burcham J: Characteristics of childhood sexual abuse and adult psychopathology in female psychiatric patients. Aust N Z J Psychiatry 31(2):200-7, 1997

Philibert R: Merging genetic and environmental effects in the Iowa Adoption Studies: focus on depression. Ann Clin Psychiatry 18(4):219-22, 2006

Pickworth WB, Fant RV: Endocrine effects of nicotine administration, tobacco and other drug withdrawal in humans. Psychoneuroendocrinology 23(2):131-41, 1998

Pico-Alfonso MA: Psychological intimate partner violence: the major predictor of posttraumatic stress disorder in abused women. Neurosci Biobehav Rev 29(1):181-93, 2005

Pincus HA, Pettit AR: The societal costs of chronic major depression. J Clin Psychiatry 62 Suppl 6:5-9, 2001

Pitman RK, Orr SP: Twenty-four hour urinary cortisol and catecholamine excretion in combat-related posttraumatic stress disorder. Biol Psychiatry 27(2):245-7, 1990

Pitts AF, Samuelson SD, Meller WH, Bissette G, Nemeroff CB, Kathol RG: Cerebrospinal fluid corticotropin-releasing hormone, vasopressin, and oxytocin concentrations in treated patients with major depression and controls. Biol Psychiatry. 38:330-5, 1995

Plichta SB, Duncan MM, Plichta L: Spouse abuse, patient-physician communication, and patient satisfaction. Am J Prev Med 12(5):297-303, 1996

Plotsky PM: Hypothalamic secretion of somatostatin and growth hormone-releasing factor into the hypophysial-portal circulation is reduced in streptozotocin diabetic male rats. Neuroendocrinology 53(5):433-8, 1991

Plotsky PM, Meaney MJ: Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. Brain Res Mol Brain Res 18(3):195-200, 1993

Plotsky PM, Owens MJ, Nemeroff CB: Psychoneuroendocrinology of depression. Hypothalamic-pituitary-adrenal axis. Psychiatr Clin North Am. 21:293-307, 1998

Plotsky PM, Thrivikraman KV, Nemeroff CB, Caldji C, Sharma S, Meaney MJ: Long-term consequences of neonatal rearing on central corticotropin-releasing factor systems in adult male rat offspring. Neuropsychopharmacology 30(12):2192-204, 2005

Post RM: Kindling and sensitization as models for affective episode recurrence, cyclicity, and tolerance phenomena. Neurosci Biobehav Rev, 2007

Post RM, Findling RL, Kahn RS: Interfaces between seizures and affective disorders: the uses of visually mapping the evolution and longitudinal course of an illness. Mt Sinai J Med 58(4):310-23, 1991

Potter E, Behan DP, Fischer WH, Linton EA, Lowry PJ, Vale WW: Cloning and characterization of the cDNAs for human and rat corticotropin releasing factor-binding proteins. Nature 349(6308):423-6, 1991

Potter E, Behan DP, Linton EA, Lowry PJ, Sawchenko PE, Vale WW: The central distribution of a corticotropin-releasing factor (CRF)-binding protein predicts multiple sites and modes of interaction with CRF. Proc Natl Acad Sci U S A 89(9):4192-6, 1992

Potter E, Sutton S, Donaldson C, Chen R, Perrin M, Lewis K, Sawchenko PE, Vale W: Distribution of corticotropin-releasing factor receptor mRNA expression in the rat brain and pituitary. Proc Natl Acad Sci U S A 91(19):8777-81, 1994

Pribor EF, Dinwiddie SH: Psychiatric correlates of incest in childhood. Am J Psychiatry 149(1):52-6, 1992

Priou A, Oliver C, Grino M: In situ hybridization of arginine vasopressin (AVP) heteronuclear ribonucleic acid reveals increased AVP gene transcription in the rat hypothalamic paraventricular nucleus in response to emotional stress. Acta Endocrinol (Copenh) 128(5):466-72, 1993

Pryce CR, Ruedi-Bettschen D, Dettling AC, Weston A, Russig H, Ferger B, Feldon J: Long-term effects of early-life environmental manipulations in rodents and primates: Potential animal models in depression research. Neurosci Biobehav Rev 29(4-5):649-74, 2005

Purba JS, Hoogendijk WJ, Hofman MA, Swaab DF: Increased number of vasopressin- and oxytocin-expressing neurons in the paraventricular nucleus of the hypothalamus in depression. Arch Gen Psychiatry 53(2):137-43, 1996

Putnam FW: Ten-year research update review: child sexual abuse. J Am Acad Child Adolesc Psychiatry 42(3):269-78, 2003

Raadsheer FC, van Heerikhuize JJ, Lucassen PJ, Hoogendijk WJ, Tilders FJ, Swaab DF: Corticotropin-releasing hormone mRNA levels in the paraventricular nucleus of patients with Alzheimer's disease and depression. Am J Psychiatry 152(9):1372-6, 1995

Rabadan-Diehl C, Lolait SJ, Aguilera G: Regulation of pituitary vasopressin V1b receptor mRNA during stress in the rat. J Neuroendocrinol 7(12):903-10, 1995

Radomsky NA: The association of parental alcoholism and rigidity with chronic illness and abuse among women. J Fam Pract 35(1):54-60, 1992

Rapaport MH, Frevert T, Babior S, Zisook S, Judd LL: A comparison of demographic variables, symptom profiles, and measurements of functioning in symptomatic volunteers and an outpatient clinical population. Psychopharmacol Bull 31(1):111-4, 1995

Raphael KG, Chandler HK, Ciccone DS: Is childhood abuse a risk factor for chronic pain in adulthood? Curr Pain Headache Rep 8(2):99-110, 2004

Raskind M, Orenstein H, Weitzman RE: Vasopressin in depression. Lancet 1(8108):164, 1979

Rasmusson AM, Lipschitz DS, Wang S, Hu S, Vojvoda D, Bremner JD, Southwick SM, Charney DS: Increased pituitary and adrenal reactivity in premenopausal women with posttraumatic stress disorder. Biol Psychiatry 50(12):965-77, 2001

Ratka A, Sutanto W, Bloemers M, de Kloet ER: On the role of brain mineralocorticoid (type I) and glucocorticoid (type II) receptors in neuroendocrine regulation. Neuroendocrinology 50(2):117-23, 1989

Regier DA, Farmer ME, Rae DS, Myers JK, Kramer M, Robins LN, George LK, Karno M, Locke BZ: One-month prevalence of mental disorders in the United States and sociodemographic characteristics: the Epidemiologic Catchment Area study. Acta Psychiatr Scand 88(1):35-47, 1993

Reinherz HZ, Giaconia RM, Pakiz B, Silverman AB, Frost AK, Lefkowitz ES: Psychosocial risks for major depression in late adolescence: a longitudinal community study. J Am Acad Child Adolesc Psychiatry 2(6):1155-63, 1993

Reinherz HZ, Paradis AD, Giaconia RM, Stashwick CK, Fitzmaurice G: Childhood and adolescent predictors of major depression in the transition to adulthood. Am J Psychiatry 160(12):2141-7, 2003

Resnick HS, Yehuda R, Pitman RK, Foy DW: Effect of previous trauma on acute plasma cortisol level following rape. Am J Psychiatry 152(11):1675-7, 1995

Reul JM, de Kloet ER: Two receptor systems for corticosterone in rat brain: microdistribution and differential occupation. Endocrinology 117(6):2505-11, 1985

Reul JM and Holsboer F: Corticotropin-releasing factor receptors 1 and 2 in anxiety and depression. Curr Opin Pharmacol 2:23-33, 2002

Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Whorwood CB, Phillips DI: Altered control of cortisol secretion in adult men with low birth weight and cardiovascular risk factors. J Clin Endocrinol Metab 86(1):245-50, 2001

Ribeiro SC, Tandon R, Grunhaus L, Greden JF: The DST as a predictor of outcome in depression: a meta-analysis. Am J Psychiatry. 150:1618-29, 1993

Riggs DS, Dancu CV, Gershuny BS, Greenberg D, Foa EB. Anger and posttraumatic-stress-disorder in female crime victims. J Traumatic Stress 5(4): 613-625, 1992

Rinne T, de Kloet ER, Wouters L, Goekoop JG, DeRijk RH, van den Brink W: Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. Biol Psychiatry 52(11):1102-12, 2002

Risbrough VB, Stein MB: Role of corticotropin releasing factor in anxiety disorders: a translational research perspective. Horm Behav 50(4):550-61, 2006

Risch SC, Golshan S, Rapaport MH, Dupont R, Outenreath R, Gillin JC, Janowsky DS: Neuroendocrine effects of intravenous ovine corticotropin-releasing factor in affective disorder patients and normal controls. Biol Psychiatry. 23:755-8, 1988

Risch SC, Lewine RJ, Kalin NH, Jewart RD, Risby ED, Caudle JM, Stipetic M, Turner J, Eccard MB, Pollard WE: Limbic-hypothalamic-pituitary-adrenal axis activity and ventricular-to-brain ratio studies in affective illness and schizophrenia. Neuropsychopharmacology 6(2):95-100, 1992

Ritchie JC, Belkin BM, Krishnan KR, Nemeroff CB, Carroll BJ: Plasma dexamethasone concentrations and dexamethasone suppression test. Biol Psychiatry 27:159-173, 1991

Rivest S: How circulating cytokines trigger the neural circuits that control the hypothalamic-pituitary-adrenal axis. Psychoneuroendocrinology 26(8):761-88, 2001

Rivier C: Role of gaseous neurotransmitters in the hypothalamic-pituitary-adrenal axis. Ann N Y Acad Sci 933:254-64, 2001

Rivier C, Vale W: Modulation of stress-induced ACTH release by corticotropin-releasing factor, catecholamines and vasopressin. Nature 305(5932):325-7, 1983

Roberts SJ: The sequelae of childhood sexual abuse: a primary care focus for adult female survivors. Nurse Pract 21(12 Pt 1):42, 45, 49-52, 1996

Rodriguez N, Ryan SW, Rowan AB, Foy DW: Posttraumatic stress disorder in a clinical sample of adult survivors of childhood sexual abuse. Child Abuse Negl 20(10):943-52, 1996

Roesler TA, McKenzie N: Effects of childhood trauma on psychological functioning in adults sexually abused as children. J Nerv Ment Dis 182(3):145-50, 1994

Rohleder N, Joksimovic L, Wolf JM, Kirschbaum C: Hypocortisolism and increased glucocorticoid sensitivity of pro-Inflammatory cytokine production in Bosnian war refugees with posttraumatic stress disorder. Biol Psychiatry 55(7):745-51, 2004

Rolls ET: Neurons in the cortex of the temporal lobe and in the amygdala of the monkey with responses selective for faces. Hum Neurobiol 3(4):209-22, 1984

Romero LM, Levine S, Sapolsky RM: Adrenocorticotropin secretagog release: stimulation by frustration and paradoxically by reward presentation. Brain Res 676(1):151-6, 1995

Romero LM, Levine S, Sapolsky RM: Patterns of adrenocorticotropin secretagog release in response to social interactions and various degrees of novelty. Psychoneuroendocrinology 20(2):183-91, 1995

Romero LM, Sapolsky RM: Patterns of ACTH secretagog secretion in response to psychological stimuli. J Neuroendocrinol 8(4):243-58, 1996

Rosenberg SD, Drake RE, Mueser K: New directions for treatment research on sequelae of sexual abuse in persons with severe mental illness. Community Ment Health J 32(4):387-400, 1996

Ross, CA: Borderline personality disorder and dissociation. J Trauma Dissociation 8(1):71-80, 2007

Rothbaum BO, Foa EB, Riggs DS, Murdock T, Walsh W: A prospective examination of posttraumatic-stress-disorder in rape victims. J Traumatic Stress 5(3):455-475, 1992

Rubin RT, Poland RE, Gouin PR, Tower BB: Secretion of hormones influencing water and electrolyte balance (antidiuretic hormone, aldosterone, prolactin) during sleep in normal adult men. Psychosom Med 40(1):44-59, 1978

Ruggiero DA, Underwood MD, Rice PM, Mann JJ, Arango V: Corticotropic-releasing hormone and serotonin interact in the human brainstem: behavioral implications. Neuroscience 91(4):1343-54, 1999

Ruggiero KJ, Smith DW, Hanson RF, Resnick HS, Saunders BE, Kilpatrick DG, Best CL: Is disclosure of childhood rape associated with mental health outcome? Results from the National Women's Study. Child Maltreat 9(1):62-77, 2004

Rumstein-McKean O, Hunsley J: Interpersonal and family functioning of female survivors of childhood sexual abuse. Clin Psychol Rev 21(3):471-90, 2001

Rupprecht R, Kornhuber J, Wodarz N, Lugauer J, Gobel C, Riederer P, Beckmann H: Lymphocyte glucocorticoid receptor binding during depression and after clinical recovery. J Affect Disord. 22:31-5, 1991

Rupprecht R, Wodarz N, Kornhuber J, Wild K, Schmitz B, Braner HU, Muller OA, Riederer P, Beckmann H: In vivo and in vitro effects of glucocorticoids on lymphocyte proliferation in depression. Eur Arch Psychiatry Clin Neurosci. 241:35-40, 1991

Rush AJ, Giles DE, Schlesser MA, Orsulak PJ, Weissenburger JE, Fulton CL, Fairchild CJ, Roffwarg HP: Dexamethasone response, thyrotropin-releasing hormone stimulation, rapid eye movement latency, and subtypes of depression. Biol Psychiatry 41(9):915-28, 1997

Russell DEH: The Secret Trauma: Incest in the Lives of Girls and Women, New York, NY, Basic Books, 1986

Rybakowski JK, Twardowska K: The dexamethasone/corticotropin-releasing hormone test in depression in bipolar and unipolar affective illness. J Psychiatr Res. 33:363-70, 1999

Salata RA, Jarrett DB, Verbalis JG, Robinson AG: Vasopressin stimulation of adrenocorticotropin hormone (ACTH) in humans. In vivo bioassay of corticotropin-releasing factor (CRF) which provides evidence for CRF mediation of the diurnal rhythm of ACTH. J Clin Invest 81(3):766-74, 1988

Sallee FR, Nesbitt L, Dougherty D, Hilal R, Nandagopal VS, Sethuraman G: Lymphocyte glucocorticoid receptor: predictor of sertraline response in adolescent major depressive disorder (MDD). Psychopharmacol Bull. 31:339-45, 1995
Sapolsky RM: Atrophy of the hippocampus in posttraumatic stress disorder: how and when? Hippocampus 11(2):90-1, 2001

Sapolsky RM: The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. Biol Psychiatry 48(8):755-65, 2000

Sapolsky RM: Why Zebras Don't Get Ulcers. New York, NY, WH Freeman and Company, 2004

Sar V, Akyuz G, Dogan O: Prevalence of dissociative disorders among women in the general population. Psychiatry Res 149(1-3):169-76, 2007

Sar V, Akyuz G, Kugu N, Ozturk E, Ertem-Vehid H: Axis I dissociative disorder comorbidity in borderline personality disorder and reports of childhood trauma. J Clin Psychiatry 67(10):1583-90, 2006

Sarkola T, Adlercreutz H, Heinonen S, Eriksson CJ: Alcohol intake, androgen and glucocorticoid steroids in premenopausal women using oral contraceptives: an interventional study. J Steroid Biochem Mol Biol 78(2):157-65, 2001

Saunders BE, Villeponteaux LA, Lipovsky JA, Kilpatrick DG, Veronen LJ: Child sexual assault as a risk factor for mental-disorders among women – a community survey. J Interpersonal Violence 7(2):189-204, 1992

Sawchenko PE, Swanson LW, Vale WW: Co-expression of corticotropin-releasing factor and vasopressin immunoreactivity in parvocellular neurosecretory neurons of the adrenalectomized rat. Proc Natl Acad Sci U S A 81(6):1883-7, 1984

Saylors K, Daliparthy N: Violence against Native women in substance abuse treatment. Am Indian Alsk Native Ment Health Res 13(1):32-51, 2006

Schaaf KK, McCanne TR: Relationship of childhood sexual, physical, and combined sexual and physical abuse to adult victimization and posttraumatic stress disorder. Child Abuse Negl 22(11):1119-33, 1998

Schlechte JA, Sherman B: Lymphocyte glucocorticoid receptor binding in depressed patients with hypercortisolemia. Psychoneuroendocrinology. 10:469-74, 1985

Schmitt TK, Mousa SA, Brack A, Schmidt DK, Rittner HL, Welte M, Schafer M, Stein C: Modulation of peripheral endogenous opioid analgesia by central afferent blockade. Anesthesiology 98(1):195-202, 2003

Schneider R, Baumrind N, Kimerling R: Exposure to child abuse and risk for mental health problems in women. Violence Vict 22(5):620-31, 2007

Schnurr PP, Friedman MJ, Rosenberg SD: Premilitary MMPI scores as predictors of combat-related PTSD symptoms. Am J Psychiatry 150(3):479-83, 1993

Schumacher JA, Coffey SF, Stasiewicz PR: Symptom severity, alcohol craving, and age of trauma onset in childhood and adolescent trauma survivors with comorbid alcohol dependence and posttraumatic stress disorder. Am J Addict 15(6):422-5, 2006

Scott LV, Dinan TG: Vasopressin as a target for antidepressant development: an assessment of the available evidence. J Affect Disord 72(2):113-24, 2002

Scott LV, Dinan TG: Vasopressin and the regulation of hypothalamic-pituitary-adrenal axis function: implications for the pathophysiology of depression. Life Sci 62(22):1985-98, 1998

Sedney MA, Brooks B: Factors associated with a history of childhood sexual experience in a nonclinical female population. J Am Acad Child Psychiatry 23(2):215-8, 1984

Seedat S, Stein DJ: Trauma and post-traumatic stress disorder in women: a review. Int Clin Psychopharmacol 15 Suppl 3:S25-33, 2000

Seedat S, Stein MB, Kennedy CM, Hauger RL: Plasma cortisol and neuropeptide Y in female victims of intimate partner violence. Psychoneuroendocrinology 28(6):796-808, 2003

Seeman TE, Singer B, Wilkinson CW, McEwen B: Gender differences in age-related changes in HPA axis reactivity. Psychoneuroendocrinology 26(3):225-40, 2001

Seckl JR, Meaney MJ: Glucocorticoid "programming" and PTSD risk. Ann N Y Acad Sci 1071:351-78, 2006

Selye H: Stress and the general adaptation syndrome. Br Med J 1(4667):1383-92, 1950

Serradeil-Le Gal C, Wagnon J, Simiand J, Griebel G, Lacour C, Guillon G, Barberis C, Brossard G, Soubrie P, Nisato D, Pascal M, Pruss R, Scatton B, Maffrand JP, Le Fur G: Characterization of (2S,4R)-1-[5-chloro-1-[(2,4-dimethoxyphenyl)sulfonyl]-3-(2-methoxy-phenyl)-2-oxo-2,3-dihydro-1H-indol-3-yl]-4-hydroxy-N,N-dimethyl-2-pyrrolidine carboxamide (SSR149415), a selective and orally active vasopressin V1b receptor antagonist. J Pharmacol Exp Ther 300(3):1122-30, 2002

Shalev A, Bleich A, Ursano RJ: Posttraumatic stress disorder: somatic comorbidity and effort tolerance. Psychosomatics 31(2):197-203, 1990

Shalev AY, Freedman S, Peri T, Brandes D, Sahar T: Predicting PTSD in trauma survivors: prospective evaluation of self-report and clinician-administered instruments. Br J Psychiatry 170:558-64, 1997

Shalev AY, Freedman S, Peri T, Brandes D, Sahar T, Orr SP, Pitman RK: Prospective study of posttraumatic stress disorder and depression following trauma. Am J Psychiatry 155(5):630-7, 1998

Shalev AY, Peri T, Canetti L, Schreiber S: Predictors of PTSD in injured trauma survivors: a prospective study. Am J Psychiatry 153(2):219-25, 1996

Shea A, Walsh C, Macmillan H, Steiner M: Child maltreatment and HPA axis dysregulation: relationship to major depressive disorder and post traumatic stress disorder in females. Psychoneuroendocrinology 30(2):162-78, 2005

Shin LM, Orr SP, Carson MA, Rauch SL, Macklin ML, Lasko NB, Peters PM, Metzger LJ, Dougherty DD, Cannistraro PA, Alpert NM, Fischman AJ, Pitman RK: Regional cerebral blood flow in the amygdala and medial prefrontal cortex during traumatic imagery in male and female Vietnam veterans with PTSD. Arch Gen Psychiatry 61(2):168-76, 2004

Siegmund A, Wotjak CT: Toward an animal model of posttraumatic stress disorder. Ann N Y Acad Sci 1071:324-34, 2006

Smith MA, Davidson J, Ritchie JC, Kudler H, Lipper S, Chappell P, Nemeroff CB: The corticotropin-releasing hormone test in patients with posttraumatic stress disorder. Biol Psychiatry 26(4):349-55, 1989

Smith PH, Gittelman DK: Psychological consequences of battering. Implications for women's health and medical practice. N C Med J 55(9):434-9, 1994

Sörenson PS, Gjerris A, Hammer M: Cerebral fluid vasopressin in neurological and psychiatric disorders. J Neurol Neurosurg Psychiatry 48:50-57, 1985

Spencer RL, Kim PJ, Kalman BA, Cole MA: Evidence for mineralocorticoid receptor facilitation of glucocorticoid receptor-dependent regulation of hypothalamic-pituitary-adrenal axis activity. Endocrinology.139:2718-26, 1998

Spertus IL, Yehuda R, Wong CM, Halligan S, Seremetis SV: Childhood emotional abuse and neglect as predictors of psychological and physical symptoms in women presenting to a primary care practice. Child Abuse Negl 27(11):1247-58, 2003

Springs FE, Friedrich WN: Health risk behaviors and medical sequelae of childhood sexual abuse. Mayo Clin Proc 67(6):527-32, 1992

Steckler T, Holsboer F, Reul JM: Glucocorticoids and depression. Baillieres Best Pract Res Clin Endocrinol Metab. 13:597-614, 1999

Stein DJ, Zungu-Dirwayi N, van Der Linden Gj, Seedat S: Pharmacotherapy for posttraumatic stress disorder. Cochrane Database Syst Rev CD002795, 2000

Stein MB, Lang AJ, Laffaye C, Satz LE, Lenox RJ, Dresselhaus TR: Relationship of sexual assault history to somatic symptoms and health anxiety in women. Gen Hosp Psychiatry 26(3):178-83, 2004

Stein MB, Simmons AN, Feinstein JS, Paulus MP: Increased amygdala and insula activation during emotion processing in anxiety-prone subjects. Am J Psychiatry 164(2):318-27, 2007

Stein MB, Walker JR, Forde DR: Gender differences in susceptibility to posttraumatic stress disorder. Behav Res Ther 38(6):619-28, 2000

Stein MB, Yehuda R, Koverola C, Hanna C: Enhanced dexamethasone suppression of plasma cortisol in adult women traumatized by childhood sexual abuse. Biol Psychiatry 42(8):680-6, 1997

Steiner H, Carrion V, Plattner B, Koopman C: Dissociative symptoms in posttraumatic stress disorder: diagnosis and treatment. Child Adolesc Psychiatr Clin N Am 12(2):231-49, viii, 2003

Stenzel P, Kesterson R, Yeung W, Cone RD, Rittenberg MB, Stenzel-Poore MP: Identification of a novel murine receptor for corticotropin-releasing hormone expressed in the heart. Mol Endocrinol 9(5):637-45, 1995

Stenzel-Poore MP, Cameron VA, Vaughan J, Sawchenko PE, Vale W: Development of Cushing's syndrome in corticotropin-releasing factor transgenic mice. Endocrinology 130(6):3378-86, 1992

Stenzel-Poore MP, Heinrichs SC, Rivest S, Koob GF, Vale WW: Overproduction of corticotropin-releasing factor in transgenic mice: a genetic model of anxiogenic behavior. J Neurosci 14(5 Pt 1):2579-84, 1994

Strohle A and Holsboer F: Stress responsive neurohormones in depression and anxiety. Pharmacopsychiatry 36 Suppl 3:S207-S214, 2003

Suomi SJ: Early stress and adult emotional reactivity in rhesus monkeys. Ciba Found Symp. 156:171-83; discussion 183-8, 1991

Suris A, Lind L, Kashner TM, Borman PD, Petty F: Sexual assault in women veterans: an examination of PTSD risk, health care utilization, and cost of care. Psychosom Med 66(5):749-56, 2004

Swanson LW, Sawchenko PE: Hypothalamic integration: organization of the paraventricular and supraoptic nuclei. Annu Rev Neurosci 6:269-324, 1983

Tanoue A, Ito S, Honda K, Oshikawa S, Kitagawa Y, Koshimizu TA, Mori T, Tsujimoto G: The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. J Clin Invest 113(2):302-9, 2004

Thaller V, Vrkljan M, Hotujac L, Thakore J: The potential role of hypocortisolism in the pathophysiology of PTSD and psoriasis. Coll Antropol 23(2):611-9, 1999

Timpl P, Spanagel R, Sillaber I, Kresse A, Reul JM, Stalla GK, Blanquet V, Steckler T, Holsboer F, Wurst W: Impaired stress response and reduced anxiety in mice lacking a functional corticotropin-releasing hormone receptor 1. Nat Genet 19(2):162-6, 1998

Tizabi Y, Aguilera G: Desensitization of the hypothalamic-pituitary-adrenal axis following prolonged administration of corticotropin-releasing hormone or vasopressin. Neuroendocrinology 56(5):611-8, 1992

Tollestrup K, Sklar D, Frost FJ, Olson L, Weybright J, Sandvig J, Larson M: Health indicators and intimate partner violence among women who are members of a managed care organization. Prev Med 29(5):431-40, 1999

Tsigos C, Chrousos GP: Hypothalamic-pituitary-adrenal axis, neuroendocrine factors and stress. J Psychosom Res 53(4):865-71, 2002

True WR, Rice J, Eisen SA, Heath AC, Goldberg J, Lyons MJ, Nowak J: A twin study of genetic and environmental contributions to liability for posttraumatic stress symptoms. Arch Gen Psychiatry 50(4):257-64, 1993

Turnbull AV, Smith GW, Lee S, Vale WW, Lee KF, Rivier C: CRF type I receptor-deficient mice exhibit a pronounced pituitary-adrenal response to local inflammation. Endocrinology 140(2):1013-7, 1999

Ullman SE: Relationship to perpetrator, disclosure, social reactions, and PTSD symptoms in child sexual abuse survivors. J Child Sex Abus 16(1):19-36, 2007

Ullman SE, Siegel JM: Victim-offender relationship and sexual assault. Violence Vict 8(2):121-34, 1993

Ullman SE, Townsend SM, Starzynski LL, Long LM: Correlates of comorbid PTSD and polysubstance use in sexual assault victims. Violence Vict 21(6):725-43, 2006

Vale W, Spiess J, Rivier C, Rivier J: Characterization of a 41-residue ovine hypothalamic peptide that stimulates secretion of corticotropin and beta-endorphin. Science 213(4514):1394-7, 1981

Valentino RJ, Van Bockstaele E: Corticotrophin-releasing factor: putative neurotransmitter actions of a neurohormone, in Hormones, Brain and Behavior, Volume 4. Edited by Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT, New York, NY, Academic Press, 2002, pp 81-103

Van Bockstaele EJ, Bajic D, Proudfit H, Valentino RJ: Topographic architecture of stress-related pathways targeting the noradrenergic locus coeruleus. Physiol Behav 73(3):273-83, 2001

van der Kolk BA, Fisler RE: Childhood abuse and neglect and loss of self-regulation. Bull Menninger Clin 58(2):145-68, 1994

van der Kolk BA, Pelcovitz D, Roth S, Mandel FS, McFarlane A, Herman JL: Dissociation, somatization, and affect dysregulation: the complexity of adaptation of trauma. Am J Psychiatry 153(7 Suppl):83-93, 1996

van der Kolk BA, Perry JC, Herman JL: Childhood origins of self-destructive behavior. Am J Psychiatry 148(12):1665-71, 1991

van Londen L, Goekoop JG, van Kempen GM, Frankhuijzen-Sierevogel AC, Wiegant VM, van der Velde EA, De Wied D: Plasma levels of arginine vasopressin elevated in patients with major depression. Neuropsychopharmacology 17(4):284-92, 1997

van Londen L, Kerkhof GA, van den Berg F, Goekoop JG, Zwinderman KH, Frankhuijzen-Sierevogel AC, Wiegant VM, de Wied D: Plasma arginine vasopressin and motor activity in major depression. Biol Psychiatry 43(3):196-204, 1998

van Rossum EF, Lamberts SW: Glucocorticoid resistance syndrome: A diagnostic and therapeutic approach. Best Pract Res Clin Endocrinol Metab 20(4):611-26, 2006

Vaughn B, Egeland B, Sroufe LA, Waters E: Individual differences in infant-mother attachment at twelve and eighteen months: stability and change in families under stress. Child Dev 50(4):971-5, 1979

Veijola J, Puukka P, Lehtinen V, Moring J, Lindholm T, Vaisanen E: Sex differences in the association between childhood experiences and adult depression. Psychol Med 28(1):21-7, 1998

Vermetten E, Bremner JD: Circuits and systems in stress. I. Preclinical studies. Depress Anxiety 15(3):126-47, 2002

Vermetten E, Bremner JD: Circuits and systems in stress. II. Applications to neurobiology and treatment in posttraumatic stress disorder. Depress Anxiety 16(1):14-38, 2002

von Bardeleben U, Holsboer F: Effect of age on the cortisol response to human corticotropin-releasing hormone in depressed patients pretreated with dexamethasone. Biol Psychiatry 29(10):1042-50, 1991

Wassef AA, O'Boyle M, Gardner R, Rose RM, Brown A, Harris A, Nguyen H, Meyer WJ 3rd: Glucocorticoid receptor binding in three different cell types in major depressive disorder: lack of evidence of receptor binding defect. Prog Neuropsychopharmacol Biol Psychiatry. 16:65-78, 1992

Weaver TL and Clum GA: Interpersonal violence: expanding the search for long-term sequelae within a sample of battered women. J Traumatic Stress 9:783-803, 1996

Weiss JM, Stout JC, Aaron MF, Quan N, Owens MJ, Butler PD, Nemeroff CB: Depression and anxiety: role of the locus coeruleus and corticotropin-releasing factor. Brain Res Bull. 35:561-72, 1994

Webster MJ, O'Grady JO, Orthmann J, Shannon Weickert C: Decreased glucocorticoid mRNA levels in individuals with depression , bipolar disorder, and schizophrenia. Schizophr Res 41:111, 2000

Weninger SC, Muglia LJ, Jacobson L, Majzoub JA: CRH-deficient mice have a normal anorectic response to chronic stress. Regul Pept 84(1-3):69-74, 1999

Whalley LJ, Borthwick N, Copolov D, Dick H, Christie JE, Fink G: Glucocorticoid receptors and depression. Br Med J (Clin Res Ed). 292:859-61, 1986

Whitnall MH: Stress selectively activates the vasopressin-containing subset of corticotropin-releasing hormone neurons. Neuroendocrinology 50(6):702-7, 1989

Whitnall MH, Key S, Gainer H: Vasopressin-containing and vasopressin-deficient

subpopulations of corticotropin-releasing factor axons are differentially affected by adrenalectomy. Endocrinology 120(5):2180-2, 1987

Whitnall MH, Smyth D, Gainer H:Vasopressin coexists in half of the corticotropin-releasing factor axons present in the external zone of the median eminence in normal rats. Neuroendocrinology 5(5):420-4, 1987

Whitworth JA, Williamson PM, Mangos G, Kelly JJ: Cardiovascular consequences of cortisol excess. Vasc Health Risk Manag 1(4):291-9, 2005

Widerlov E, Bissette G, Nemeroff CB: Monoamine metabolites, corticotropin releasing factor and somatostatin as CSF markers in depressed patients. J Affect Disord. 14:99-107, 1988

Widiger TA, Anderson KG: Personality and depression in women. J Affect Disord 74(1):59-66, 2003

Widom CS: Posttraumatic stress disorder in abused and neglected children grown up. Am J Psychiatry 156(8):1223-9, 1999

Wiersma A, Bohus B, Koolhaas JM: Corticotropin-releasing hormone microinfusion in the central amygdala diminishes a cardiac parasympathetic outflow under stress-free conditions. Brain Res 625(2):219-27, 1993

Wiersma A, Konsman JP, Knollema S, Bohus B, Koolhaas JM: Differential effects of CRH infusion into the central nucleus of the amygdala in the Roman high-avoidance and low-avoidance rats. Psychoneuroendocrinology 23(3):261-74, 1998

Wijma B, Schei B, Swahnberg K, Hilden M, Offerdal K, Pikarinen U, Sidenius K, Steingrimsdottir T, Stoum H, Halmesmaki E; Nordic cross-sectional study: Emotional, physical, and sexual abuse in patients visiting gynaecology clinics: a Nordic cross-sectional study. Lancet 361(9375):2107-13, 2003

Williams JB: Standardizing the Hamilton Depression Rating Scale: past, present, and future. Eur Arch Psychiatry Clin Neurosci 251 Suppl 2:II6-12, 2001

Willner P: Validity, reliability and utility of the chronic mild stress model of depression: a 10-year review and evaluation. Psychopharmacology (Berl) 134(4):319-29, 1997

Wilt S, Olson S: Prevalence of domestic violence in the United States. J Am Med Womens Assoc 51(3):77-82, 1996

Wolfe DA, Sas L, Wekerle C: Factors associated with the development of posttraumatic stress disorder among child victims of sexual abuse. Child Abuse Negl 18(1):37-50, 1994

Wong CM, Yehuda R: Sex Differences in Post-Traumatic Stress Disorder, in Psychiatric Illness in Women, Emerging Treatments and Research. Edited by Lewis-Hall F, Williams TS, Panetta JA, Herrrra JM, Washington, DC, American Psychiatric Publishing Inc, 2002, pp 57-98

Woods SJ: Prevalence and patterns of posttraumatic stress disorder in abused and postabused women. Issues Ment Health Nurs 21(3):309-24, 2000

Woods SJ, Campbell JC: Posttraumatic stress in battered women: does the diagnosis fit? Issues Ment Health Nurs 14(2):173-86, 1993

Yamada K, Tamura Y, Yoshida S: Effect of administration of corticotropin-releasing hormone and glucocorticoid on arginine vasopressin response to osmotic stimulus in normal subjects and patients with hypocorticotropinism without overt diabetes insipidus. J Clin Endocrinol Metab 69(2):396-401, 1989

Yehuda R, Boisoneau D, Lowy MT, Giller EL Jr: Dose-response changes in plasma cortisol and lymphocyte glucocorticoid receptors following dexamethasone administration in combat veterans with and without posttraumatic stress disorder. Arch Gen Psychiatry 52(7):583-93, 1995

Yehuda R, Boisoneau D, Mason JW, Giller EL: Glucocorticoid receptor number and cortisol excretion in mood, anxiety, and psychotic disorders. Biol Psychiatry. 34:18-25, 1993

Yehuda R, Halligan SL, Golier JA, Grossman R, Bierer LM: Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder. Psychoneuroendocrinology 29(3):389-404, 2004

Yehuda R, Halligan SL, Grossman R, Golier JA, Wong C: The cortisol and glucocorticoid receptor response to low dose dexamethasone administration in aging combat veterans and holocaust survivors with and without posttraumatic stress disorder. Biol Psychiatry 52(5):393-403, 2002

Yehuda R, Kahana B, Binder-Brynes K, Southwick SM, Mason JW, Giller EL: Low urinary cortisol excretion in Holocaust survivors with posttraumatic stress disorder. Am J Psychiatry 152(7):982-6, 1995

Yehuda R, Lowy MT, Southwick SM, Shaffer D, Giller EL Jr: Lymphocyte glucocorticoid receptor number in posttraumatic stress disorder. Am J Psychiatry 148(4):499-504, 1991

Yehuda R, McFarlane AC, Shalev AY: Predicting the development of posttraumatic stress disorder from the acute response to a traumatic event. Biol Psychiatry 44(12):1305-13, 1998

Yehuda R, Resnick HS, Schmeidler J, Yang RK, Pitman RK: Predictors of cortisol and 3-methoxy-4-hydroxyphenylglycol responses in the acute aftermath of rape. Biol Psychiatry 43(11):855-9, 1998

Yehuda R, Southwick SM, Krystal JH, Bremner D, Charney DS, Mason JW: Enhanced suppression of cortisol following dexamethasone administration in posttraumatic stress disorder. Am J Psychiatry 150(1):83-6, 1993

Yehuda R, Teicher MH, Levengood RA, Trestman RL, Siever LJ: Circadian regulation of basal cortisol levels in posttraumatic stress disorder. Ann N Y Acad Sci 746:378-80, 1994

Young AH: Antiglucocoticoid treatments for depression. Aust N Z J Psychiatry 40(5):402-5, 2006

Young EA, Liberzon I: Stress and Anxiety Disorders, in Hormones, Brain and Behavior, Volume 5. Edited by Pfaff DW, Arnold AP, Etgen AM, Fahrbach SE, Rubin RT, New York, NY, Academic Press, 2002, pp 443-465

Young EZ, Abelson JL, Curtis GC, Nesse RM: Childhood adversity and vulnerability to mood and anxiety disorders. Depression and Anxiety 5:66-72, 1997

Young MA, Fogg LF, Scheftner WA, Fawcett JA: Concordance of symptoms in recurrent depressive episodes. J Affect Disord 20(2):79-85, 1990

Zaidi LY, Foy DW: Childhood abuse experiences and combat-related PTSD. J Trauma Stress. 7(1):33-42, 1994

Zanarini MC, Frankenburg FR, Reich DB, Marino MF, Haynes MC, Gunderson JG: Violence in the lives of adult borderline patients. J Nerv Ment Dis 187(2):65-71, 1999

Zhou JN, Riemersma RF, Unmehopa UA, Hoogendijk WJ, van Heerikhuize JJ, Hofman MA, Swaab DF: Alterations in arginine vasopressin neurons in the suprachiasmatic nucleus in depression. Arch Gen Psychiatry 58(7):655-62, 2001

Zlotnick C, Johnson DM, Stout RL, Zywiak WH, Johnson JE, Schneider RJ: Childhood abuse and intake severity in alcohol disorder patients. J Trauma Stress 19(6):949-59, 2007

Zlotnick C, Mattia J, Zimmerman M: Clinical features of survivors of sexual abuse with major depression. Child Abuse Negl 25(3):357-67, 2001

Zlotnick C, Pearlstein T: Validation of the structured interview for disorders of extreme stress. Compr Psychiatry 38(4):243-7, 1997

Zlotnick C, Shea MT, Begin A, Pearlstein T, Simpson E, Costello E: The validation of the Trauma Symptom Checklist-40 (TSC-40) in a sample of inpatients. Child Abuse Negl 20(6):503-10, 1996

Zlotnick C, Warshaw M, Shea MT, Allsworth J, Pearlstein T, Keller MB: Chronicity in posttraumatic stress disorder (PTSD) and predictors of course of comorbid PTSD in patients with anxiety disorders. J Trauma Stress 12(1):89-100, 1999

Zlotnick C, Zakriski AL, Shea MT, Costello E, Begin A, Pearlstein T, Simpson E: The long-term sequelae of sexual abuse: support for a complex posttraumatic stress disorder. J Trauma Stress 9(2):195-205, 1996

Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, Holsboer F: Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 34(3):171-81, 2000

Zobel AW, Nickel T, Sonntag A, Uhr M, Holsboer F, Ising M: Cortisol response in the combined dexamethasone/CRH test as predictor of relapse in patients with remitted depression. a prospective study. J Psychiatr Res. 35:83-94, 2001

Zobel AW, Yassouridis A, Frieboes RM, Holsboer F: Prediction of medium-term outcome by cortisol response to the combined dexamethasone-CRH test in patients with remitted depression. Am J Psychiatry 156:949-51, 1999

Zoellner LA, Foa EB, Brigidi BD: Interpersonal friction and PTSD in female victims of sexual and nonsexual assault. J Trauma Stress 12(4):689-700, 1999

Zoellner LA, Goodwin ML, Foa EB: PTSD severity and health perceptions in female victims of sexual assault. J Trauma Stress 13(4):635-49, 2000

Zoumakis E, Rice KC, Gold PW, Chrousos GP: Potential uses of corticotropin-releasing hormone antagonists. Ann N Y Acad Sci 1083:239-51, 2006

Zunzunegui MV, Beland F, Llacer A, Leon V: Gender differences in depressive symptoms among Spanish elderly. Soc Psychiatry Psychiatr Epidemiol 33(5):195-205, 1998

Zuravin SJ, Fontanella C: Parenting behaviors and perceived parenting competence of child sexual abuse survivors. Child Abuse Negl 23(7):623-32, 1999